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THE RELATION OF INHALATION ANALGESIA AND ANESTHESIA TO ASPHYXIA NEONATORUM*

CURTIS J. LUND, M.S., M.D., MADISON, WIS.

(From the Department of Obstetrics and Gynecology, University of Wisconsin, and the State of Wisconsin General Hospital)

FREEDOM from asphyxia neonatorum should constitute one of the important properties of an ideal obstetric inhalation analgesic or anesthetic agent. Nevertheless, we must recognize that this is but one of the necessary and desirable qualities. Guedel[1] has defined an ideal anesthetic agent for obstetrics as one that "should have no ill effect, immediate or remote, upon either the mother or the baby. It should render true physical relief from suffering, and should be applicable over a long period of time without influence upon uterine contraction. It must present to the obstetrician a patient in satisfactory condition for correct delivery, and to be practical it must admit of convenient and simple application."

It would be presumptuous for an obstetrician to speak with authority concerning the physiology, pharmacology, and clinical management of obstetric anesthesia. The converse would be equally as true. Yet there is an intermediate zone in which the knowledge and experiences of both must be integrated, and it is on this common ground that we must meet while discussing this material. The subject must be limited to the

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relationship of various inhalation agents to asphyxia neonatorum rather than a general consideration of obstetric inhalation agents.

Notwithstanding the voluminous literature concerning obstetric anesthesia there is a paucity of actual data about its influence on asphyxia neonatorum. Many of the older reports dismissed the subject with a general statement or two without attempting to study its many ramifications. Recent investigators have begun an attack on the problem in a systematic manner.

Cole and others,[2] Henderson and collaborators,[3] and Heard[4] are of the opinion that ether or some of its combinations, when used as obstetric anesthetic agents, definitely increase asphyxia neonatorum, while Embree[5] found little asphyxia definitely attributable to either ether or chloroform. Nitrous oxide and cyclopropane were both superior to ether, in Heard's estimation, but he obtained the least asphyxia neonatorum following spinal anesthesia for cesarean section. Much has been written about nitrous oxide and asphyxia neonatorum, particularly during the past few years when the full significance of its relation to oxygen deficiency was appreciated. Davis[6] and Clifford and Irving[7] noted that nitrous oxide may be given for long periods of time without significant effect on the newborn infant. Plass and Swanson[8] in a comparative study of ethylene and nitrous oxide in obstetrics stated that there was a greater incidence of asphyxia neonatorum following the use of nitrous oxide. The increase, however, was in the mild type of asphyxia. Very little statistical material has appeared regarding cyclopropane. After studying a small series of cases, Smith[9] was of the opinion that the agent was very readily and quickly transmitted to the infant. He was not prepared to state any definite conclusions as to its value in obstetrics.

MATERIALS AND METHODS

As a part of a general survey of the etiologic factors of asphyxia neonatorum, the department of anesthesia generously cooperated by permitting the use of their detailed records of anesthesia. These were

TABLE I. CLASSIFICATION OF ASPHYXIA NEONATORUM AS USED IN THIS STUDY

PHYSICAL SIGNS		NO ASPHYXIA	MILD ASPHYXIA	MODERATE ASPHYXIA	SEVERE* ASPHYXIA
Respiratory	Onset respiration	Spontaneous Immediate	Spontaneous oligopnea 1-5 min.	Delayed apnea 5-15 min.	Delayed apnea over 15 min.
	Resuscitation	None	None	Tracheal tube or mouth-to-mouth	Tracheal tube or mouth-to-mouth
Activity	Cry	Vigorous Lusty	Delayed Vigorous Lusty	Delayed Weak	Weak or absent
Cyanosis		None	Mild	Moderate	Severe or pallor
Muscular activity		Vigorous Active	Sluggish	Depressed	Flaccid and relaxed
Pallor and/or shock		None	None	None	Present

*All infants alive at onset of labor but who died during labor are included in this group.

combined with the obstetric data and then recorded by the punch-card method. A complete record of 1,982 deliveries was obtained. All of the deliveries were in this hospital and were immediately supervised by trained resident obstetricians and anesthetists or by permanent staff members, a fact which lends uniformity and accuracy to the records. Table I shows the classification of asphyxia neonatorum used for this study. The use of the punch-card system necessitates accurate definitions of the conditions to be recorded. Usually the criteria have varied according to the personal views of the particular investigator, and therefore we have adhered to the classification which has proved satisfactory in our experience. It is unfortunate that so many exist. Occasionally incomplete records may have led to minor errors in classification of the mild types of asphyxia, but in the "moderate" and "severe" groups the data have been uniform. Because of the necessity for brevity and clarity, the "moderate" and "severe" forms will occasionally be combined into a single unit called "dangerous" asphyxia which will differentiate it from the "mild" group.

In a previous publication,[10] it was observed that prematurity, complications of pregnancy and labor, methods of delivery, and misuse of analgesics were some of the more important causes of asphyxia neonatorum. Each of these factors must be considered in any investigation of inhalation agents.

Because of the variation in detail of treatment of each case, it is difficult to determine the contribution of inhalation agents to the incidence of asphyxia neonatorum. In general, however, the following methods were used. In the majority of uncomplicated term pregnancies, the individual received moderate amounts of nonvolatile analgesic drugs, usually opiates, during the early part of the first stage of labor. Later in the first stage and during the second stage of labor nitrous oxide was commonly used as an inhalation analgesic, and it was given intermittently with contractions by a semiclosed technique. Nitrous oxide, cyclopropane, and ethylene were used at the time of delivery in concentrations such as to produce surgical anesthesia as opposed to analgesia. Nitrous oxide and ethylene were used for some simple operative procedures. At the present time the less potent agents such as nitrous oxide and ethylene are rarely used for operative deliveries, instead cyclopropane and occasionally ether or chloroform are given. Ether and chloroform were chiefly used when conditions demanded complete relaxation for operative obstetrics or in cases of emergency when other equipment was unavailable.

The judicious management of the patient thus gives rise to so many variables that the results require circumspect analysis. In spite of these many variables certain interesting and significant facts appear.

RESULTS

The total cases have been divided into six groups according to the type of inhalation agents received (Table II). In the nitrous oxide

TABLE II. ASPHYXIA NEONATORUM IN RELATION TO INHALATION AGENTS

AGENT	NO. CASES	NO ASPHYXIA PER CENT	MILD ASPHYXIA PER CENT	MODERATE ASPHYXIA PER CENT	SEVERE ASPHYXIA PER CENT
Nitrous oxide	1,115	89.0	6.0	4.0	1.0
Nitrous oxide and ethylene	133	85.0	8.5	3.0	3.5
Nitrous oxide and cyclopropane	319	83.5	7.5	7.0	2.0
Cyclopropane	181	67.5	9.5	17.0	6.0
Others	69	76.5	4.5	12.0	7.5
None	165	84.5	7.0	6.0	2.0
Grand total	1,982	85.0	6.8	6.0	2.2

group are placed all patients receiving that agent alone, usually as an analgesic agent. Two other groups received nitrous oxide as an analgesic agent, but it was supplemented either by ethylene or by cyclopropane as anesthetic agents for delivery. A fourth group had no preliminary analgesia and the patients were anesthetized with cyclopropane. This group embraced a series of complicated cases which, for the most part, were delivered operatively either vaginally or by cesarean section. The fifth group designated "others" was made up of patients receiving ether, chloroform, and an occasional local or spinal anesthesia. This group was small and heterogeneous and of little statistical significance. The final group were those having no inhalation agents, frequently not by choice but because of other factors, including precipitate delivery.

TABLE III. INHALATION AGENTS AND TYPE OF DELIVERY

AGENT	SPONTANEOUS				OPERATIVE			
	NUMBER CASES	NONE PER CENT	MILD PER CENT	MODERATE AND SEVERE	NUMBER CASES	NONE PER CENT	MILD PER CENT	MODERATE AND SEVERE
N_2O	997	90.0	6.0	4.0	118	79.0	7.5	13.5
N_2O C_2H_4	36	91.5	5.3	3.0	97	82.5	9.5	8.0
N_2O C_3H_6	111	88.5	7.0	4.5	208	81.0	7.5	11.5
C_3H_6	22	91.0	0.0	9.0	159	63.5	10.5	26.0
Others	27	89.0	7.0	4.0	41	68.0	2.5	29.0
None	165	86.0	6.0	8.0				
	LOW FORCEPS				OTHER VAGINAL OPERATIONS			
N_2O	85	79.0	8.0	13.0	33	79.0	3.0	18.0
N_2O C_2H_4	67	83.5	7.5	9.0	17	88.0	6.0	6.0
N_2O C_3H_6	162	84.0	7.0	9.0	44	70.5	9.0	20.5
C_3H_6	20	70.0	5.0	25.0	17	66.5	8.5	25.0
Others	10	80.0	0.0	20.0	20	50.0	5.0	45.0

Method of Delivery.—An analysis of similar methods of delivery with each of the several agents indicate that the given procedure is more significant in the production of asphyxia than is the anesthetic agent. For example (Table III) all spontaneous deliveries show about the same amount of moderate and severe asphyxia neonatorum, approximately 4 per cent, whether the analgesic agent was nitrous oxide, ethylene, cyclopropane, or others.

Low forceps delivery was used only upon definite clinical indications. It thus differs somewhat from the outlet or prophylactic forceps delivery which is in common use. In this group, it is interesting to note that the best results were obtained when nitrous oxide was used as a preliminary analgesic agent and ethylene or cyclopropane used as the anesthetic agent for delivery. When nitrous oxide alone was used for forceps delivery, the incidence of fetal asphyxia was higher, probably because the concentration of nitrous oxide necessary for surgical anesthesia gives rise to fetal anoxia.

A comparison of all operative deliveries gives the same general results except for the apparent paradox in the two groups of patients that received cyclopropane for anesthesia. In one group anesthesia was preceded by nitrous oxide analgesia while the patient was bearing down with her contractions; in the other group, the patient was immediately anesthetized with cyclopropane and delivery consummated. The latter group included most of the cesarean sections, a method of delivery atraumatic to the fetus. The nitrous oxide-cyclopropane group all had vaginal operative delivery with its attendant trauma to the fetus. Subsequent data will give some information about this discrepancy.

Type of Delivery and Premedication.—By minimizing the influence of nonvolatile analgesics and trauma of delivery, both etiologically significant factors in asphyxia neonatorum, it is possible to gain some definite data about the inhalation analgesic agents. It can be seen (Fig. 1) that in unpremedicated spontaneous deliveries asphyxia neonatorum is at a minimum regardless of the type of inhalation agent employed. Some of the groups contained so few cases that they have little statistical value, but the results, such as they are, tend to support the conclusions drawn from the larger series. These are that the type of delivery and premedication are more significant in asphyxia neonatorum than is the type of inhalation agent. One other point should be considered, this again concerns the two cyclopropane groups. In the unpremedicated operative series the incidence of dangerous asphyxia for the two cyclopropane groups is similar and relatively low. However, following premedication, the incidence increases. This study is being extended to cesarean section where apparently similar results are being analyzed.

Prematurity.—It has been previously shown[10] that prematurity is one of the outstanding factors in any study of asphyxia neonatorum. The question that immediately arises is: Are prematures more sensitive to a certain inhalation agent, to all inhalation agents, or to none? Because of the rather limited number of premature deliveries (approximately 15 for each agent in each of the seventh and eighth months of pregnancy),

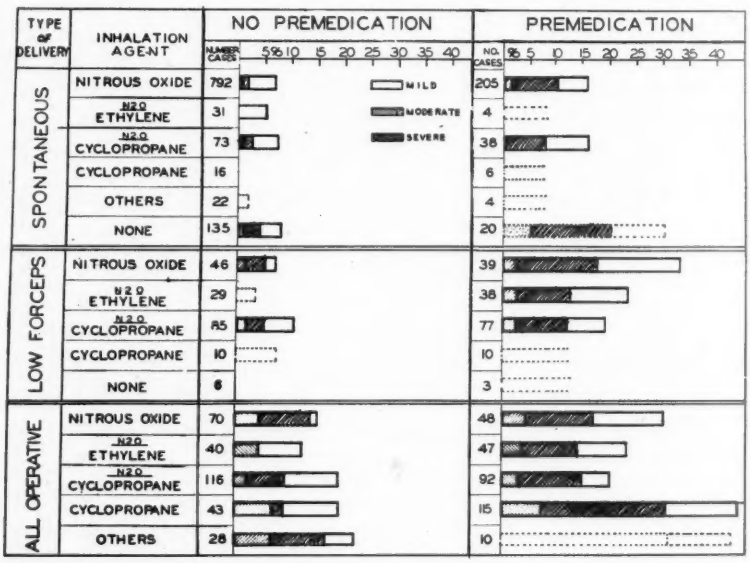

Fig. 1.—Chart showing that with various agents there is little difference in incidence of asphyxia neonatorum when the cases are separated according to delivery and premedication.

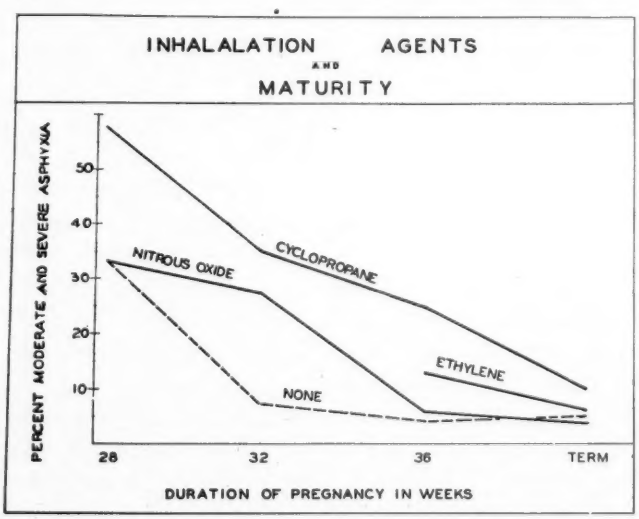

Fig. 2.—The very young prematures have asphyxia regardless of agents. By thirty-two weeks those having no inhalation agents were less susceptible to asphyxia. At thirty-six weeks all agents but cyclopropane were well tolerated by the infant. At term all agents were similar in effect on asphyxia neonatorum.

the results are not conclusive. However, the indications are that, at the twenty-eighth week of gestation, the inherent fragility of the fetus offsets any effects of the inhalation agents. At the thirty-second week those infants having no inhalation agents were definitely superior to others. But, by the thirty-sixth week this sensitivity was no longer demonstrable except for cyclopropane. At term there was little difference; however, the more potent agent cyclopropane still gave evidence of greater asphyxia (Fig. 2).

Complications of Pregnancy.—The unusually large number of cases presenting some type of complication of pregnancy or labor made it possible to demonstrate the marked effect that they have on neonatal asphyxia. In many instances it was not the complications per se that

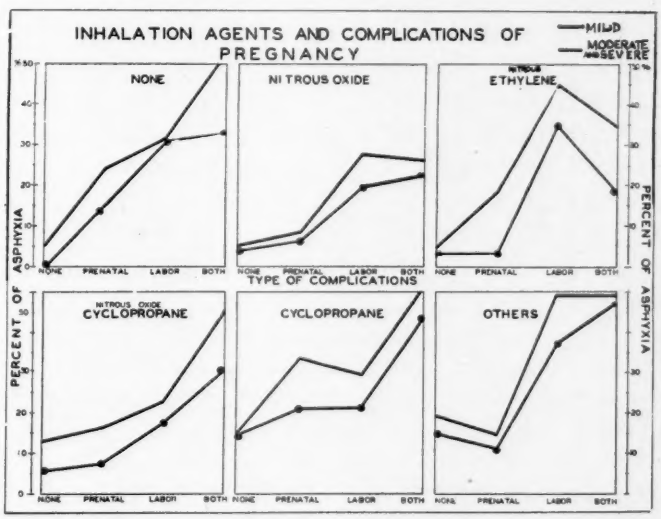

Fig. 3.—Complications of prenatal period and of labor are more significant in the production of asphyxia than are the inhalation agents. The incidence of "mild" and "dangerous" asphyxia neonatorum under each of these conditions is evident.

were responsible for the asphyxia but their influence on the conduct of labor. Among 728 complicated cases and 1,251 uncomplicated ones, dangerous asphyxia was three times as common in the former group. For comparative purposes these two groups were subdivided into four: (1) patients with no complications, (2) those showing prenatal complications only, (3) patients with complications during labor only, and finally (4) those having both prenatal complications and complications of labor. In Group 1 the combined moderate and severe asphyxia neonatorum was 5 per cent; in Group 2, 10 per cent; in Group 3, 20 per cent; and in Group 4, 30 per cent. As can be seen (Fig. 3), the mild type of asphyxia is remarkably constant under all conditions, a fact which has been repeatedly observed in all of our analyses. This has raised the question as to the significance of that class; perhaps it

is an inherent accompaniment of labor that would be unavoidably present under all circumstances. The influence of complications on asphyxia neonatorum can be seen at a glance. Further analysis of those uncomplicated cases show that there is little dangerous asphyxia in the groups receiving no agents, nitrous oxide or ethylene. There is some increase in the group receiving cyclopropane or "other" agents. This may be due in part to the agents. Most of these patients had operative delivery and that would add another factor.

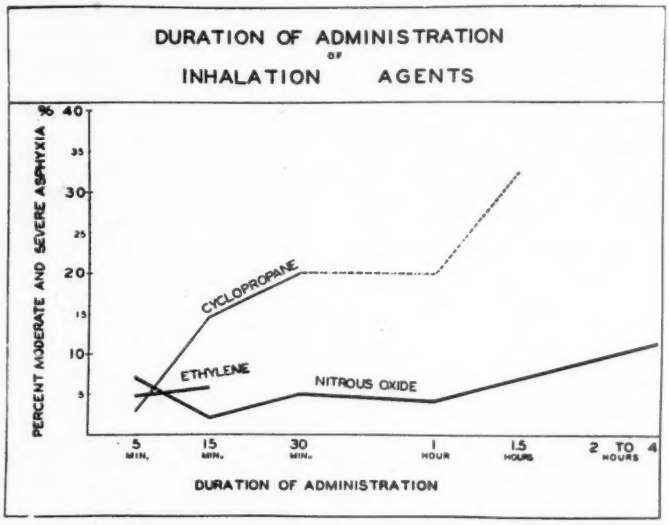

Fig. 4.—Prolonged administration of cyclopropane quickly increases the incidence of asphyxia. Nitrous oxide may be given for long periods of time with little increase in asphyxia neonatorum.

Duration of Administration of Agents.—There seems to be a striking difference in the effects of various agents on the fetus when administered for varying periods of time. Because of this difference each agent must be analyzed singly. Nitrous oxide administration was followed by increased asphyxia only when given for very short or for very long periods of time (Fig. 4). The short periods of administration were usually associated with rapidly progressing labors with tumultuous pains and delivery imminent. Increasing the concentration of nitrous oxide at this point in order to obtain pain relief or to prevent delivery reduced the oxygen content of the blood reaching the fetus, with resulting asphyxia. This particular point was repeatedly verified by observing slowing of the fetal heart rate as oxygen want intervened. This increase in asphyxia, coincident with prolonged administration, may or may not have been the fault of the gas. There is an increase in incidence of asphyxia neonatorum with prolongation of the second stage of labor beyond one and one-half hours, and this rather than the nitrous oxide was probably the etiologic factor. In a group

of 50 cases without prolongation of the second stage of labor, nitrous oxide was given from three to twelve hours with little increase of "dangerous" asphyxia.

Ethylene was not given for long periods of time but these data would indicate that it was slightly superior to nitrous oxide when given for five minutes but slightly inferior when given for fifteen minutes. Cyclopropane was in distinct contrast to the other agents. With it neonatal asphyxia was at its minimum when administration was limited to five minutes; in fact, at this time interval it surpassed the other agents under consideration. Asphyxia increased rapidly as the time of administration increased. After fifteen minutes the "moderate" and "severe" asphyxia had increased from 3.5 to 14 per cent and at the end of thirty minutes' administration it was 20 per cent.

Technique of Administration.—Anesthetic techniques do not ordinarily concern the obstetrician, so they will not be discussed at length. There was no correlation between technique of administration and asphyxia neonatorum. The following data about nitrous oxide are typical of results we have obtained: Semiclosed technique (with some rebreathing), 971 cases with 6 per cent "dangerous" asphyxia; closed absorption technique, 94 cases with 6.5 per cent; and McKesson technique, 466 cases with 7 per cent asphyxia.

Others.—Numerous other correlations have been made, yet none of them add significant details to this study. In passing, however, two of them should be mentioned. The first is that of parity. As would be expected, there was greater incidence of asphyxia in the first born than in those of subsequent pregnancies, but this was unrelated to the inhalation agents used. It is interesting to note that there were 610 multiparas having nitrous oxide as the sole analgesic agent. In this group there was but 1.0 per cent "severe" asphyxia, and 1.5 per cent moderate asphyxia, or a total of 2.5 per cent of "dangerous" asphyxia.

Further studies were made to correlate the duration of the first and second stages of labor. Again there was no significant relation to inhalation agents. When the first stage of labor was prolonged beyond thirty to thirty-six hours, there was an increase in incidence of asphyxia neonatorum regardless of the agent used at termination of labor. Likewise, when the second stage was longer than one and one-half or two hours, there was an increase in asphyxia neonatorum irrespective of the inhalation agents used.

DISCUSSION

Nitrous oxide.—Like most of the analgesic and anesthetic agents, nitrous oxide has had its periods of popularity and decline. The early literature was summarized by Davis[11] in 1916. Since that time nitrous oxide has been in general use. Eastman's observations[12] that dangerous

fetal oxygen want existed when nitrous oxide was given to the mother in concentrations of 90 per cent or more have caused many to discard the agent. This is an unfortunate occurrence. The average trained anesthetist will in most cases have little difficulty in giving nitrous oxide analgesia without significant fetal oxygen want. Furthermore, even the less expert anesthetist may be reasonably well assured that no dangerous fetal oxygen want exists as long as the fetal heart rate remains within normal limits. Our results indicate that nitrous oxide may be given for long periods of time as an analgesic agent without danger. When asphyxia neonatorum occurs after use of nitrous oxide, the agent has been used incorrectly, without sufficient oxygen, for some procedure requiring a more appropriate agent.

Ethylene.—This agent has had extensive use in the midwest as an analgesic and anesthetic agent. From the point of view of asphyxia neonatorum, our studies would indicate that it was as satisfactory as nitrous oxide for purposes of analgesia. In this series it was used as an anesthetic agent only for some simple operative procedures in which it was superior to nitrous oxide and compared favorably with cyclopropane. Our observations would indicate that with proper regard for oxygen concentrations ethylene may be given for analgesia and limited anesthesia without significant effect on the incidence of asphyxia neonatorum.

Cyclopropane.—This agent is a relative newcomer to the field of obstetric analgesia and anesthesia. Little more than opinions have been expressed in the literature. In this series of 500 administrations, the following conclusions seem warranted. As an analgesic agent cyclopropane compares favorably with nitrous oxide and ethylene in the incidence of asphyxia neonatorum. As an agent for general anesthesia, it causes some increase in the incidence of fetal asphyxia but probably no more than any other anesthetic agent. When used as an agent for general anesthesia, asphyxia neonatorum varied directly with the duration of the administration of cyclopropane. Induction is very rapid with this agent, permitting the anesthetist to have the patient anesthetized in a short time. If the obstetrician proceeds without unnecessary delay, most deliveries may be completed before the cyclopropane has had time to depress the respiratory function of the infant. In this manner the qualities of the agent may be properly utilized.

Others.—From the few cases in this group, it is hazardous to draw any definite conclusions. There are indications that, as with previous agents, general anesthesia causes some increase in asphyxia neonatorum.

SUMMARY

1982 consecutive deliveries were reviewed from the aspect of asphyxia neonatorum in relation to inhalation analgesic and anesthetic agents.

1. Nitrous oxide, ethylene, and cyclopropane, when used as analgesic agents, did not materially influence the incidence of asphyxia neonatorum.

2. Nitrous oxide, properly administered, was given for long periods of time without significant effects on fetal asphyxia.

3. Cyclopropane and other agents when used in concentrations sufficient for anesthesia by operative delivery were accompanied by an increase in the incidence of fetal asphyxia.

4. The incidence of asphyxia neonatorum varied directly as the duration of administration of cyclopropane anesthesia.

5. There seemed to be no relationship between asphyxia neonatorum and the type of anesthetic technique.

6. Prematurity, complications of pregnancy and labor, method of delivery and misuse of analgesic agents were apparently of greater significance in asphyxia neonatorum than the various inhalation agents when properly administered.

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DISCUSSION

DR. RHETT McMAHON, Baton Rouge, La.—The essayist has certainly presented an extraordinary series of cases and his conclusions are so well backed up by facts that they offer little opportunity for discussion. However, I feel that all anesthetic agents do influence the production of anoxemia. Even nitrous oxide if prolonged will produce asphyxia, mild in degree at first, but when pushed to the stage of anesthesia, the asphyxia increases. Our experience with ethylene was so unsatisfactory on account of several dangerous cases of asphyxia that it is not used in our service at all. With nitrous oxide we have had more experience, and it is our choice for analgesia.

The time element is so important, especially when doing cesarean section, that we now have our patient completely prepared before the administration of our anesthesia. In that way we reduce the amount used and feel we have reduced the asphyxia.

The body of this paper clearly proves one of the author's opening statements, namely, that we have no ideal obstetric analgesic procedure. We are often stampeded into the injudicious use of these agents by lay pressure. It is incumbent upon meetings like this fully to inform the public of the status of these problems.

Patients should be told that in spite of what *Time Magazine, Life* and the *Ladies' Home Journal* say, we have no ideal obstetric analgesia, that there is no such thing as a safe, painless delivery, and that many children are being sacrificed today because this is not fully appreciated.

DR. JAMES R. MANLEY, DULUTH, MINN.—We have some trouble every once in a while with general anesthetics in forceps delivery, principally because the patients are not prepared for anesthesia. They have been given something to eat and the stomach is full, when the doctor decides to apply forceps. These patients have difficulty with cyanosis and vomiting. I wonder if the baby is not asphyxiated if the mother is cyanotic for five or ten minutes during the delivery.

I saw one case recently in consultation. The patient had been cyanotic for a while, and aspiration of the trachea was necessary. The baby was born dead, but the autopsy showed no injury and the fetal heart had been all right during the early part of the anesthesia. Does Dr. Lund believe that such cyanosis in the mother contributes to asphyxia in the baby?

DR. JOHN F. KELLY, INDIANAPOLIS, IND.—I would like to put in a word for local anesthesia as I have used it in a considerable number of cases after having been first forced to its use in a patient with heart failure some years ago. Lately I have been using it less perhaps because a patient has to be watched closely in order to start the local nerve block procedure at the proper time.

Most of my experience has been with pudendal block and an occasional experience with parasacral block. The resident at the Coleman Hospital ran a series of 50 cases last year using a method of sacral block. He introduced a ureteral catheter into the sacral canal and left it there until the perineal stage, so that at any time the novocain solution could be injected. Technically I found this difficult but it worked well in the hands of this resident.

Local anesthesia can be used very satisfactorily on private patients and the baby breathes spontaneously as if nothing were used to relieve pain. Pudendal block can sometimes be started within two hours of an instillation of rectal ether and the patient remembers nothing of the performance. If the pudendal block is not sufficient for outlet forceps, it at least reduces the amount of general anesthesia to a very few minutes and the episiotomy can be repaired without anything else.

DR. LUND (closing).—As to Dr. McMahon's question I think there is no doubt that gas by itself may have some effect on asphyxia neonatorum. In this series of cases we had no opportunity to study normal cases without gas analgesia so our study would add little in this respect to our previous knowledge.

One point that I want to bring out is the excellent quality of anesthetists which we have in our institution. This is the answer to many of our problems, and this is why we have had such good results in many of these cases.

As to Dr. Manley's question, I have made the same observation; namely, in a baby which died in utero following a period of extreme maternal cyanosis. If there is maternal cyanosis we can usually expect asphyxia of the infant. When maternal cyanosis occurs in the course of delivery I think it well to postpone delivery until the cyanosis has been cleared up. Undoubtedly trauma of delivery in the presence of oxygen want adds to the hazard, so for that reason it is better, I believe, to correct the maternal oxygen want and then proceed with the delivery.

We have had little experience with local anesthesia. Dr. Henderson's presentation before this Society last year discussed that problem very satisfactorily.

RADIUM IN THE TREATMENT OF UTERINE BLEEDING CAUSED BY BENIGN LESIONS*

LAWRENCE M. RANDALL, M.D., SIM B. LOVELADY, M.D., AND FLETCHER S. SLUDER, M.D., ROCHESTER, MINN.

(From the Section on Obstetrics and Gynecology, Mayo Clinic and Mayo Foundation)

COMPLETE follow-up records were studied on 196 women who experienced atypical uterine bleeding (menorrhagia and/or metrorrhagia) caused by benign conditions, five or more years after treatment by radium or roentgen rays. These treatments were administered by the section on therapeutic radiology of the Mayo Clinic. Our results are given on the basis of satisfactory control of the bleeding, and for the younger women we have considered also the preservation of menstrual and reproductive function. In all cases treatment was preceded by dilatation and curettage and microscopic examination of the endometrium removed.

Atypical uterine bleeding frequently occurs in the first half of the reproductive life of women. In these cases the initial treatment should always aim to regulate and preserve the menstrual function. Such methods of treatment are known to all and need not be enlarged on in this paper. In certain cases all conservative forms of treatment fail and more radical measures must be adopted as a means of preserving the health or saving the life of the patient. When conservative methods of treatment fail and no evidence of pathologic change of the pelvic viscera can be found, small amounts of radium may be applied in the uterine cavity. A considerable experience with doses of from 150 to 300 mc. hours for women less than thirty years of age has shown a fair percentage of success. Not infrequently menstruation has become fairly regular in amount and interval and some patients have borne children thereafter. If this form of treatment should fail, hysterectomy can be performed subsequently. Stacy and Mussey[1] previously have discussed this group of patients.

Although it is not possible to draw an arbitrary age limit, it is frequently more difficult to regulate gross abnormalities of menstruation by conservative measures after the age of thirty years. After this age, myomatous changes in the uterus become more common and may interfere with the results of conservative treatment. The end results of old pelvic inflammatory disease begin to occur and the function of the ovaries begins to wane. Nevertheless, until the age of forty years is

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reached, physicians are reluctant to inhibit ovarian function permanently unless this measure is necessary to preserve the health of the individual. For patients between thirty and forty years of age, an attempt is often made to achieve control of atypical uterine bleeding by a submenopausal dose of radium. This procedure is used particularly for patients in the early part of the fourth decade of life. In the latter part of this decade more and more patients are given a menopausal dose when radium is used. When increased amounts of radium are employed, temporary or permanent inhibition of function of the ovaries will occur more frequently. When the usual general symptoms of the menopause do appear and require treatment with estrogenic substances after irradiation therapy, often the chance of recurrence of atypical uterine bleeding which then may require further treatment is increased. Furthermore, the younger the ovary the greater its recuperative capacity. Consequently a certain percentage of women less than forty years of age who receive a calculated menopausal dose of radium will subsequently have spontaneous recurrence of atypical uterine bleeding which may necessitate further treatment.

REVIEW OF LITERATURE

The literature contains many contributions in which the relative merits of surgical and radiation treatment of this condition are debated. Ward[2] suggested 1,800 mg. hours for patients more than forty years of age. Corscaden[3] in a recent report used from 600 to 2,400 mg. hours for patients less than thirty-eight years, and 3,000 mg. hours for patients more than thirty-eight years when associated fibroids had enlarged the uterus to the size of two and one-half months of pregnancy. Brown and his associates[4] employed dosages of roentgen rays from 125 to 1,000 r. They felt that it takes 625 to 749 r. to assure permanent cessation of menstrual function. Corscaden expressed the belief that 300 r. anteriorly and 300 r. posteriorly will cause amenorrhea for a period of six to eight months in the case of women less than thirty years of age but that the same dosage may cause permanent amenorrhea among women more than thirty-eight years, and that 600 r. will sterilize most women. In their study the initial doses of radium ranged from 250 mg. hours to 1,200+ mg. hours. The dose employed for most women at or near the menopause was 1,200 mg. hours.

Keene and Payne[5] studied 423 cases of functional uterine bleeding. After tabulating the results of radium used to control the bleeding in 391 cases, they came to the conclusion that in at least 50 per cent some other form of treatment was required. They reported one death for which the treatment could not be held responsible. Their mortality rate following hysterectomy was 0.5 per cent. They stated that surgical treatment with conservation of ovarian tissue will be followed by severe menopausal symptoms in 7 per cent of cases. In their experience, treatment with radium of women thirty years of age or less resulted in restoration of menstruation to normal in 88 per cent of cases; permanent amenorrhea occurred in 6 per cent and severe menopausal symptoms in 8 per cent. Of forty married women in this group, 5 gave birth to normal babies and 8 had miscarriages after irradiation. For patients between thirty and forty years of age the picture changed. Bleeding of 95 per cent was

controlled; 24 per cent had permanent amenorrhea and 21 per cent severe menopausal symptoms. With initial doses of 200 to 300 mg. hours of radium, the bleeding of 80 per cent was controlled without permanent amenorrhea or severe menopausal symptoms. When 800 to 1,200 mg. hours of radium were given, permanent amenorrhea occurred in 56 per cent and severe menopausal symptoms in 47 per cent. In this group, 10 pregnancies occurred among 70 patients which resulted in 6 normal babies and 4 miscarriages. With a dose of 1,200 mg. hours, the bleeding of women aged forty to fifty years was controlled in 97 per cent of cases but severe menopausal symptoms occurred in 38 per cent. In their experience radium therapy approached perfection when the patients were between the ages of fifty and sixty years.

Norris and Behney[6] found in 1,437 cases of hemorrhage from the uterus caused by benign conditions that in 750 cases bleeding was due to functional causes and in 687 cases myomas were present. Satisfactory results were obtained in 83 per cent by the use of radium; in 3 per cent bleeding recurred in ten years or more. Carcinoma developed after irradiation in 1.09 per cent. About the same proportion of satisfactory results were obtained in cases in which myomas were present as in cases of functional hemorrhage. The mortality rate in the entire group was 0.278 per cent.

Rousseau[7] reported the findings in 841 cases of uterine bleeding caused by functional conditions, the menopause, or fibroids. He came to the conclusion that fibroids contributed to the bleeding in more than 50 per cent of cases. He stated that in 5 per cent of cases in which treatment with radium was employed operation may be required later, and in 95 per cent satisfactory results should be obtained from radium.

On the other hand Heaney,[8] Gough,[9] Suggs,[10] Schlink,[11] Squire and Allen,[12] and others have favored hysterectomy to a menopausal dose of radium or roentgen rays, especially for women less than forty years of age, and have stated that in most instances elective operation is less radical than irradiation.

Corscaden recently reported a series of 733 cases of atypical uterine bleeding that occurred with or without uterine myomas; these cases had been traced for an average of eight years. The bleeding was controlled with radium or roentgen rays in 719 (98.1 per cent) and uncontrolled in 14 (1.9 per cent). Supplementary irradiation was required in 30 (6.1 per cent) of 493 cases in which radium was employed and in 18 (7.6 per cent) of 240 cases in which roentgen treatment was given. Corscaden expressed the belief that the chief cause of failure in these cases was submucous myomas.

RESULTS OF STUDY OF CASES

Since the gynecologist or general surgeon is most often confronted with the question of irradiation or operation for those women who are forty years of age or less we have divided our series of 196 patients into two main groups: (1) those forty years or less of age and (2) those more than forty years of age.

The results of varying doses of radium on 79 patients forty years of age or less who did not have demonstrable myomas at the time of the initial examination or at the time of the dilatation and curettage are given in Table I. Of 79 patients, 47 (59.4 per cent) experienced satisfactory results from the initial dose of radium. An additional 10 pa-

TABLE I. RESULTS OF VARYING DOSES OF RADIUM ON PATIENTS FORTY YEARS OF AGE OR LESS WITHOUT MYOMAS

	DOSE, MG. HR.			TOTAL
	LESS THAN 500	500-1000	1000-1200 OR MORE	
Patients	20	29	30	79
Results				
Satisfactory	8	17	22	47
Unsatisfactory	12	12	8	32
Additional radium	2	3	5	10
Hysterectomy	6	5	1	12
Dilatation and curettage			1	1
Removal of ovarian tumor			1	1
No additional radium or operation; continued trouble	4	4	0	8

tients (13.5 per cent) were given subsequent radium treatments with good results. Twelve patients (15.1 per cent) required hysterectomy before the bleeding was controlled. Eight patients (10.1 per cent) had severe menopausal symptoms. Four pregnancies occurred among the 64 married women (6.2 per cent). Of 35 patients forty years of age or less who had myomas, 15 (42.8 per cent) obtained satisfactory results following the initial dose of radium (Table II). One patient had

TABLE II. RESULTS OF VARYING DOSES OF RADIUM ON PATIENTS FORTY YEARS OF AGE OR LESS WITH MYOMAS

	DOSE, MG. HR.			TOTAL
	LESS THAN 500	500-1000	1000-1200 OR MORE	
Patients	10	16	9	35
Results				
Satisfactory	2	8	5	15
Unsatisfactory	8	8	4	20
Additional radium	1	0	0	1
Hysterectomy	6	8	3	17
No additional radium or operation; continued trouble	1	0	1	2

a subsequent application of radium. Hysterectomy was subsequently performed on 17 patients (48.5 per cent) who had myomas which contributed to the bleeding. Four patients (11.4 per cent) in this group complained of severe menopausal symptoms. Of the 30 married women, only one became pregnant after treatment.

Forty-seven patients more than forty years of age were treated with radium (Table III). This includes those who had uterine fibroids and

TABLE III. RESULTS OF RADIUM ON PATIENTS MORE THAN FORTY YEARS OF AGE WITH AND WITHOUT MYOMAS

	DOSE: 1000-1200 OR MORE MG. HR.*	
	NO MYOMAS	MYOMAS
Patients	27	20
Results		
Satisfactory	25	18
Unsatisfactory	2	2
Hysterectomy	1	2
No additional radium or operation; continued trouble	1 death	

*Additional radium was not given in any case.

those who did not have them. All of these patients received doses of radium of 1,000 mg. hours or more. Of the 27 patients who did not have myomas, 92.6 per cent received satisfactory results. Four patients in this group (14.8 per cent) had severe menopausal symptoms. One patient in this group died of a pulmonary embolus on the fourteenth day after dilatation and curettage and insertion of radium into the uterus. Of 20 patients who had myomas, 90 per cent received satisfactory results. One patient (5 per cent) had severe menopausal symptoms.

The results of abdominal and vaginal applications of radium to 14 patients in both age groups are given in Table IV. In only 2 cases in

TABLE IV. RESULTS OF ABDOMINAL AND VAGINAL RADIUM ON PATIENTS IN BOTH AGE GROUPS

	AVERAGE DOSE	
	PATIENTS 40 YR. OF AGE OR LESS	PATIENTS MORE THAN 40 YR. OF AGE
	ABDOMINAL 12,000 MG. HR.	VAGINAL 800 MG. HR.
Patients	11	3
Results		
Satisfactory	9	1
Unsatisfactory	2	2
Additional radium	0	1
Hysterectomy	1	1 (Dilatation and curettage)
No additional radium or operation; continued trouble	1	0

the combined group was a diagnosis of uterine myoma made. This number was so small that these cases are classed with those in which no myomas were demonstrable. Ten (71.4 per cent) obtained satisfactory results. Two patients experienced severe menopausal symptoms, and one pregnancy occurred among the 12 married women.

In 21 cases of functional uterine bleeding roentgen therapy was employed (Table V). Even with the smaller doses the results in this

TABLE V. RESULTS FOLLOWING ROENTGEN THERAPY

	DOSAGE, ROENTGENS*				
	PATIENTS MORE THAN 40 YR. OF AGE			PATIENTS 40 YR. OF AGE OR LESS	
	700	960	1680	525-960	1242-1760
Patients	1	4	3	7	6
Results					
Satisfactory	1	4	3	6	5
Unsatisfactory	0	0	0	1	1
Additional roentgen treatment	0	0	0	0	1
Hysterectomy	0	0	0	1	0
No additional roentgen treatment or operation; continued trouble	0	0	0	0	0

*The dosage listed represents the total roentgen dosage. The number of fields varied per patient.

group were excellent. The results in 19 of the 21 cases (90.4 per cent) were satisfactory. The bleeding of all of the patients who were more than forty years of age was controlled with the initial dose of roentgen rays. Among the patients forty years of age or less one required further

roentgen therapy and one patient had a hysterectomy. There were no deaths following roentgen therapy.

We were particularly interested in what happened to the group of patients who were forty years of age or less. These cases were divided according to age and dose of radium received (Table VI).

TABLE VI. RESULTS OF RADIUM TREATMENT OF ALL PATIENTS FORTY YEARS OF AGE OR LESS

	DOSAGE, MG. HR.				
	AGES 36-40		AGES 27-35		TOTAL
	1,000 OR LESS	MORE THAN 1,000	1,000 OR LESS	MORE THAN 1,000	
Patients	37	38	38	12	125
Results					
Satisfactory	20	27	17	7	71
Unsatisfactory	17	11	21	5	54
Additional radium or x-ray	2	4	3	2	11
Hysterectomy	10	5	15	2	32
No additional radium or operation; continued trouble	5	2	3	1	11

Of the patients from thirty-six to forty years of age, inclusive, 62.7 per cent obtained satisfactory results. The bleeding of 20, or 54 per cent, of the patients in this age group who received 1,000 mg. or less hours and that of 27, or 71 per cent, of the patients in this age group who received more than 1,000 mg. hours was controlled. Of the patients aged from twenty-seven to thirty-five years inclusive approximately, 50 per cent obtained satisfactory results. The bleeding of 44.7 per cent of the patients in this age group who received 1,000 mg. hours or less of radium and that of 58.3 per cent of those who received 1,000 mg. hours or more was controlled. Of 125 patients forty years of age or less, 21 (16.8 per cent) menstruated regularly after radium therapy. The other patients in this group of 125 had either permanent amenorrhea or an occasional scanty flow.

The pregnancies of 106 married women following radiation for functional uterine bleeding are listed in Table VII. Pregnancy did not occur in the group of cases in which roentgen treatment was given.

TABLE VII. RÉSUMÉ OF PREGNANCIES FOLLOWING TREATMENT WITH RADIUM*

AGE OF PATIENT YEARS	LABOR AND RESULT
36	Premature labor at 7 months; baby died
34	Patient died at time of delivery; baby apparently normal
37	Miscarriage early in pregnancy
35	Normal pregnancy
34	One year after radiation treatment miscarriage at 3 months
	One year later premature labor at 7 months; baby died
32	Five months pregnant at time of questionnaire

*The first two patients received 1,200 mg. hours and the last four 350 to 700 mg. hours of radium. None of these patients had myomas.

Of the 106 patients, 6 (5.6 per cent) had one or more pregnancies. Of these, 2 had miscarriages and 2 had premature labors and the babies did not survive. No information was obtained concerning fetal anomalies.

Malignant lesions developed in 2 cases after irradiation. In one total abdominal hysterectomy was performed for an early adenocarcinoma of the fundus of the uterus nine years after treatment with radium. In the other panhysterectomy was performed for a fibrosarcoma and adenocarcinoma of the uterus four years after roentgen therapy.

COMMENT AND SUMMARY

The results of radiation therapy in 196 patients who had atypical uterine bleeding not caused by a malignant condition were studied. One hundred and seventy-five patients were treated with radium and 21 with roentgen rays. The bleeding was satisfactorily controlled by the initial treatment in 134 (68.4 per cent). In 13 cases (6.6 per cent) subsequent radiation therapy was necessary before the bleeding was controlled. Thus good results were obtained in 147 (75 per cent). In 34 cases (17.7 per cent of the 196 cases) hysterectomy was performed sooner or later because of persistent bleeding. Eighteen patients (9.1 per cent) complained specifically of menopausal symptoms. Six pregnancies occurred among 106 married women, an incidence of 5.6 per cent.

There were 125 patients in this group who were forty years of age or younger and were treated with radium. Twenty-one (16.8 per cent) of these established a fairly normal menstrual cycle after radium therapy. One patient in the total group died from pulmonary embolism after dilatation and curettage and intrauterine application of radium.

The percentage of good results from all types of radium treatment increased with the age of the patients. Approximately 50 per cent of those aged twenty-seven to thirty-five years, inclusive, obtained good results from radium; 62.7 per cent of those thirty-five to forty years of age, inclusive, were satisfactorily treated, and 91.4 per cent of the patients more than forty years of age obtained satisfactory results. It is evident that as the age of the patients increased the dose of radium administered tended to increase. We believe, for patients more than forty years of age without fibroids or when fibroids are present but the uterus is not enlarged to more than its size after three months of pregnancy, that preliminary dilatation and curettage for diagnosis followed by intrauterine application of a menopausal dose of radium or the administration of roentgen ray therapy are excellent forms of treatment for atypical uterine bleeding. For the group of patients who are from thirty to forty years of age, the choice of treatment is made with more difficulty. To one who is surgically minded failure of about 25 per cent from radiation in the entire series would indicate that hysterectomy accompanied by a 98 to 99 per cent possibility of cure is preferable. By this method of treatment, it is possible to preserve the function of the ovaries and at least to delay the onset of the menopause. Further, surgical treatment will allow the correction of associated conditions that occur from relaxation of the pelvic supports as well as the removal of associated lesions.

The radiologist can point to a satisfactory control of bleeding in 75 per cent of cases at an initial risk of less than 1 per cent and the avoidance of a major surgical procedure. Radiation therapy does not preclude the subsequent performance of hysterectomy should it become necessary later.

Radium is often stated to be a conservative form of treatment. This may be true in the younger age group when 250 mg. hours or less is used or in the older women when an amount calculated to produce the menopause is used near or in the climacteric when ovarian function is shortly to cease. Radium or roentgen rays may be used in preference to surgical treatment for women in the fifth decade of life suffering from atypical uterine bleeding caused by benign lesions when the natural menopause is to be anticipated shortly, when a uterus is no larger than it is in the third month of pregnancy, when the operative risk is increased because of associated conditions and when no gross evidence of active pelvic inflammatory disease exists. We doubt whether radiation therapy is truly conservative in the fourth decade of life in the treatment of atypical uterine bleeding that has failed to respond to other treatment. It seems to us that sacrifice of a uterus whose function cannot be controlled and the preservation of the ovaries is more conservative. Naturally such a statement is made on the basis of a minimal mortality rate from hysterectomy.

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DISCUSSION

DR. EARL CONWAY SMITH, New Orleans, La.—All cases of atypical uterine bleeding in the category of this series should have a *thorough* uterine curettage with microscopic examination of the tissues removed, as only by so doing can the occasional early malignancy be recognized and treated accordingly. Great emphasis should be placed upon the selection of the type of patient suitable for radium therapy. Radium should not be applied until all other more common measures have failed.

Not all will agree that radium should be used in puberal girls and women of the childbearing age due to the uncertain results which include the high incidence of miscarriages in the relatively rare pregnancies that do occur in those women that

remain fertile following its use. Through such reports we may learn to use even smaller doses of radium, thereby increasing the number who remain fertile after treatment.

Atypical bleeding in the first half of the reproductive life gives us our greatest worry when it cannot be controlled by conservative measures. Radium, when judiciously used with respect to proper selection of case and proper dosage, certainly has its field of usefulness here. The percentage of cures, even though the percentage of those establishing a regular menstrual rhythm is low after radium application, warrants its use in preference to hysterectomy, as hysterectomy can almost always be done later.

In the second half of the reproductive period (30 to 40 years), I believe the atypical bleeding cases of benign origin should be divided into two groups with respect to management. First, those patients extremely desirous of having a baby, and second, those who have their family or are known to be sterile. Both groups must, of course, be qualified by the presence or absence of definite indications or contraindications to surgery. In the first group, those desirous of becoming pregnant should be given a submenopausal dose of radium in the hope that ovarian function will be preserved. In the second group, I believe that total hysterectomy with conservation of ovarian function is the procedure of choice.

At the menopause, opinions are definite and favor the use of radium unless there are specific indications or contraindications for surgery.

Before radium is applied in any patient before the climacteric, a clear explanation should be made to that patient or to some responsible member of the family, that, although the bleeding is controlled in 60 to 90 per cent of the cases, nothing definite can be promised as to the preservation of ovarian function.

I, of course, condemn the use of radium in the fertile woman by the occasional operator.

DR. PHILIP F. SCHNEIDER, EVANSTON, ILL.—In the group of younger women, in the absence of myomas or pathology of other kinds, we must assume that the bleeding of which the patient complains is in most instances due to some endocrine imbalance. When radium is used we know that further depletion of the function of the ovary, or interference with the normal function of the ovary occurs.

While the bleeding can be controlled by hysterectomy or radium, both of these methods are usually accompanied by an exaggeration of subjective symptoms. The dosage of radium has been found to be a very important factor not only in stopping the bleeding but in relieving the subjective symptoms. Nevertheless it is to be hoped that with increased knowledge of endocrine diagnosis and therapy, the need for radium and surgery in the absence of demonstrable pathology will be appreciably decreased.

DR. GILBERT F. DOUGLAS, BIRMINGHAM, ALA.—In a group of cases which we have been working on at the Hillman Hospital in Birmingham, we have, so far as possible, avoided both radium and x-ray. In treating these cases we endeavor to delay for a period of time and if necessary do several curettages before resorting to radiation. As a result, there have been very few of these cases that could not be corrected if proper study was done to determine the endocrine status of the subject. Certainly in the younger group we should work to determine if the condition cannot be corrected by more conservative means.

DR. KARL JOHN KARNAKY, HOUSTON, TEXAS.—In the past five years we have had at the Jefferson Davis Hospital more than 500 cases of uterine bleeding sent to us and in not one case have we used radium. Our experience with patients receiving radium from other sources before coming to us has been discouraging. I recall 3 patients with functional uterine bleeding sent to me who continued to

bleed after receiving radium and only stopped when they had received stilbestrol. There were also three patients who had been given the so-called stimulating dose of radium for bleeding due to benign lesions. The first two patients were told that their menstruation would stop for only a few months, but three years afterwards there still has been no sign of a flow. The other young girl had to have a laparotomy because of bleeding from the right ovary. The left ovary was found to be entirely atrophic and the right ovary was full of old clotted blood. Several private patients who have had large doses of radium for menopausal bleeding were also sent to me and were psychologic problems. Apparently I have seen only the bad side of radium therapy.

We have been giving 5.0 to 25.0 mg. of stilbestrol to stop uterine bleeding due to benign lesions. Our results have been most gratifying. We can keep these patients from bleeding for one month, six months, or twenty-four months. One young girl, age 19 years, was made amenorrheic for approximately 2 years. She has been closely watched and studied. Many blood chemistry studies and endometrial biopsies have been taken and none of these showed anything abnormal. She has now menstruated 6 times and the endometrial biopsies have all been pre-menstrual in morphology, which indicates that ovulation had occurred. She also had a laparotomy, and grossly there were no abnormal changes observed in the uterus and tubes. The ovaries were like those seen at a full-term pregnancy, that is, they were small, smooth, and devoid of normal follicular cysts.

According to our routine we give 5.0 to 25.0 mg. of stilbestrol in oil, according to the amount of bleeding, into the anterior lip of the cervix, using a spinal needle and a 10 c.c. syringe. If, however, the patient is not bleeding very much and is in good physical condition, she is given a prescription for twenty-five 5.0 mg. stilbestrol tablets and is instructed to take one tablet every night at bedtime for twenty nights. She has 5 extra 5.0 mg. stilbestrol tablets left, and these are to be used if needed for the withdrawal bleeding, because two to eight days following the taking of the last 5.0 mg. tablet she will spot for two or three days, bleed for two or three days, and then spot for two or three days more. If this bleeding is excessive she can take one or two of the 5.0 mg. stilbestrol tablets to check the flow. In 14 to 21 days later she will start to flow again. Eighty-seven per cent of the patients will flow normally again if thyroid is given up to tolerance (pulse of 100 to 110). To reach such a dose ¼ gr. is given every morning before breakfast, and every fourth morning the dose is increased ¼ gr. until the tolerance dose is reached, whether it be ¼ or 30 gr.

The more I study normal and abnormal uterine bleeding, the more I am convinced that bleeding is dependent on an estrogenic hormonal blood level. With an estrogenic blood level above or below this normal level the patient is amenorrheic. Examples are the amenorrhea of pregnancy, which is above the estrogenic bleeding, and the absent periods of the young girl before puberty, which is below the estrogenic bleeding level.

DR. WILLIS E. BROWN, OMAHA, NEB.—I should like to report the results of our experiences in the University of Nebraska and the University of Michigan with radiation therapy. In our studies we used a relatively new unit of measuring the amount of radiation delivered. The radiologists call this the "tissue roentgen." By this means they are able to compute the exact amount of radiation delivered to the ovary. We should not group our patients by so many milligram hours of radium or roentgens of x-ray for the effectiveness of this therapy will vary with the thickness, weight, and age of the patient.

It is our experience that 1,000 mg. hours of radium in a millimeter and one-half of platinum within the uterine cavity will only give you 75 per cent cessation of the uterine bleeding. If on the other hand we raise this by 300 or 500 mg. hours

for the heavy patients, the level of success will be increased to 95 per cent. The same thing is true of x-ray. If one can deliver 600 "tissue roentgens" to the ovary almost 100 per cent success will be obtained. Radiation therapy of this type is most suitable in patients who are 40 years of age or over. When the dosage is adjusted, the degree of success approximates that of surgical management.

DR. RANDALL (closing).—I made no attempt to discuss the endocrine therapy that might be used in these patients, inasmuch as they constitute a group in which endocrine therapy had failed and in which some more radical treatment was necessary. Furthermore these patients were treated in the period from 1930 to 1935 at a time when endocrine therapy was not as well advanced as it now is.

The point of the paper was to show what results were obtained by the doses of radium employed. I am particularly pleased at the discussion about the technique of the application of radium therapy. This applies especially to the patients over forty years of age. In the group under discussion, in many instances one tries to preserve menstrual function by using submenopausal or subcastration doses of radium. It seems to sum up to the fact that these patients should be intensively studied and treated with conservative measures first and later with radical measures if necessary. I do not believe we can make a flat rule as to treatment of this younger age group.

CLINICAL EVALUATION OF EQUINE GONADOTROPIN*

LAMAN A. GRAY, M.D., LOUISVILLE, KY.

(From the Department of Obstetrics and Gynecology, University of Louisville Medical School)

GREAT clinical interest in the gonadotropic hormone from the serum of pregnant mares began with an excellent paper by Davis and Koff[1] in 1938, in which they claimed experimental ovulation in women for the first time. Thirty-six women at various stages of the menstrual cycle were given 50 to 70 units of "gonadogen" intravenously sixteen to seventy-six hours before operation. Sixteen patients had young corpora lutea. There was some skepticism of these results, but following the confirmation of Siegler[2] and others the production of ovulation in the normal or responsive ovary by this means is fairly generally accepted.

A number of papers have appeared since that time applying the hormone to clinical conditions. Unfortunately most of them have dealt with entirely clinical details in cases that might show spontaneous remissions, or with cases having such varied treatment as to leave doubt as to which may have been the effective therapeutic agent. It has seemed to us that sufficient groundwork has not been laid to advise complicated combinations of this hormone with others to obtain magic cures. Still other papers have been so enthusiastic as to be incredulous to a profession that has been so misled with chorionic gonadotropin.

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Two recent papers with well-studied cases are of interest because of their negative results.

Erving, Sears, and Rock[3] (1940) concluded that 81 per cent of their 48 patients with sterility, dysfunctional flowing or amenorrhea were apparently unaffected by the mare's serum hormone. In no case was there any definite evidence of stimulation of ovulation. Vogt and Sexton[4] (1941) reported 13 patients with amenorrhea and 4 with metrorrhagia. The patients with amenorrhea were primed with 16,000 units of estrone. Three with amenorrhea menstruated regularly and all 4 with metrorrhagia showed immediate improvement. No ovulatory effect on the endometrium was found in any case. A most important point in these two papers is that the prepared aqueous solution of the hormone (gonadin, Cutter) was used.

The present paper is intended to summarize our studies conducted over a period of three years on the dried form of this hormone (gonadogen, Upjohn). Our previously reported cases of patients with amenorrhea and metrorrhagia,[5] (1940) and primary dysmenorrhea[6] (1941) are resummarized here with a longer follow-up and additional cases. Also patients with male sterility are described, in an effort to bring together the main indications for the hormone at the present time, correlated with the results we have obtained. Throughout this work an effort has been made to use consistently the one hormone with no other therapy at the time, not because there may not be great value in combinations, but to determine any positive effects that the hormone alone may have. Thyroid has not been prescribed, although some patients would probably have been benefited by it. Clinical effects on bleeding, pain, and fertility have been noted and whenever possible endometrial biopsies or sperm counts have been obtained for objective data.

AMENORRHEA

Sixteen patients with secondary amenorrhea have been treated with the pregnant mare's serum hormone. Eleven had biopsies before treatment. Two had atrophic endometrium, 7 interval nonsecretory endometrium, and 2 endometrial hyperplasia (nonsecretory). Treatment was continued from one to nineteen months. Menstruation attributed to the hormone occurred in 12 patients. Two others menstruated three and fourteen months after treatment; in each instance the patient had received only one month's treatment. Two patients (Cases 1 and 3) were completely refractory after nine and twelve months of cyclic treatment, although one (Case 1) had one single mensis after three months.

Of the 12 who had cyclic menstruation, 6 patients showed secretory endometrium (5 normal premenstrual) after treatment, while 4 had nonsecretory endometrium. But of those who had secretory endometrium, it is interesting that as treatment continued, the majority of menses were nonsecretory. Case 2 had two cycles of secretory and two cycles of nonsecretory endometriums. Case 5 had three cycles of secretory and three cycles of nonsecretory endometriums. Case 6 had

TABLE I. AMENORRHEA

CASE	AGE	DURATION	ENDOMETRIUM	P.M.S.* UNITS	OBSERVATION	CLINICAL RESULT	FOLLOW-UP BIOPSIES
1	18	3 yr.	Atrophic	400	36 mo.	One mensis in 12 mo.	Nonsecret. 12×
2	19	6 mo.	Atrophic	260	36 mo.	Regular menses 2 yr.	Secretory 2× Nonsecret. 2×
3	21	13 mo.	Nonsecretory	710	9 mo.	No menses	Nonsecret. 8×
4	24	9 mo.	Nonsecretory	100	6 mo.	Regular menses	
5	26	5 mo.	Nonsecretory	70	16 mo.	Regular menses	Secretory 3× Nonsecret. 3×
6	23	14 mo.	Nonsecretory	930	38 mo.	Regular menses. No menses after treatment stopped	Secretory 3× Nonsecret. 9×
7	23	10 mo.	Nonsecretory	120	6 mo.	Regular menses	Secretory 1× Nonsecret. 1×
8	18	8 mo.	Hyperplasia	610	14 mo.	Regular menses	Nonsecret. or hyperplasia 10×
9	17	4 mo.		110	2 mo.	One mensis	Nonsecret. 1×
10	25	8 mo.	Nonsecretory	30	17 mo.	No menses 13 mo. Then 3 menses	Nonsecret. 1×
11	28	20 mo.	Nonsecretory	40	5 mo.	One mensis 3 mo. later	
12	19	13 mo.		610	23 mo.	Regular menses	Secretory 2× Nonsecret. 9×
13	18	9 mo.	Hyperplasia	410	16 mo.	Regular menses	
14	26	6 mo.		240		Three menses followed by pregnancy	Secretory 1×
15	20	13 mo.		60	1 mo.	Menses in 14 days	
16	35	9 mo.		180	3 mo.	Regular menses	

*P.M.S., Pregnant mare's serum.

three cycles of secretory and nine cycles of nonsecretory endometriums. Case 7 had one cycle each of secretory and nonsecretory endometriums. Case 11 had two cycles of secretory and nine cycles of nonsecretory endometriums. Case 14 had one cycle of secretory endometrium followed by a normal pregnancy and a normal child.

From these data it is evident that growth effects have occurred in the endometrium followed by secretory effects in six cases. Five patients are known to have continued cyclic menstruation over a period of months after the hormone was discontinued, and one is known to have stopped immediately after continuous treatment for twenty months. Even after ovulation apparently is established during treatment, it does not occur in the majority of cycles as treatment is continued. However these experiments seem to demonstrate that normal secretory endometrium can be brought about in the majority of the cases by the pregnant mare's serum alone.

Short summaries of four cases, which are particularly interesting in comparing two other potent products (anterior pituitary extract from sheep and a mixture containing anterior pituitary extract and chorionic gonadotropin [synapoidin]), are given. Detailed discussion of the latter products are too lengthy for this paper.

CASE 1.—Menses which began at 13 years of age were irregular until the patient reached the age of 15 when amenorrhea occurred for twenty months. Repeated biopsies showed atrophic endometrium. After

three months' treatment with gonadogen (60 units each month), the patient had one menstrual period. Gonadogen was repeated for nine months during which time the biopsies showed slight growth effect, then reverted to consistent atrophic endometrium. After twelve months of treatment, gonadogen was discontinued and anterior pituitary extract from sheep was given each month in dosages from 100 to 300 hypophysectomized rat units. After two months, the endometrium showed slight hyperplasia with no secretion and regular menstrual periods began. The anterior pituitary extract was continued every month, and biopsies before each period showed interval nonsecretory endometrium or endometrial hyperplasia with "Swiss cheese" glands. After thirteen months of steady treatment with anterior pituitary extract, late interval secretory endometrium was first obtained. After the fifteenth month normal premenstrual endometrium was found. Treatment with anterior pituitary extract was continued monthly and 8 of the next 11 consecutive monthly biopsies showed secretory endometriums. The last biopsy was nonsecretory and was the only cycle in which anterior pituitary extract had not been given in twenty-four months. In this case, the anterior pituitary extract has given normal secretory endometrium when the pregnant mare's serum was ineffective.

CASE 3.—Patient, 21 years old, had had regular menses from the age of 13 to 20, but had had none for seven months when first seen. Biopsies showed nonsecretory endometrium. Gonadogen was given each month for nine months. No menses occurred. Biopsies remained nonsecretory, at times atrophic. In the next twelve months, the patient received anterior pituitary extract from sheep. Two menses occurred. Biopsies remained nonsecretory but showed fair growth effect. In the next twelve months, the patient was given synapoidin each month. She had three menses. Biopsies taken each month showed consistently nonsecretory endometrium. The pregnant mare's serum was followed by no menses, anterior pituitary extract and synapoidin were each followed by occasional menses, but at no time did secretory endometrium occur.

CASE 6.—Patient, 23 years old, had had amenorrhea for fourteen months. Biopsies showed nonsecretory endometrium. Gonadogen was given each month for twenty months, resulting in cyclic menstruation. Secretory endometrium (twice full premenstrual) was found 3 times and nonsecretory 9 times. Menses stopped after two months. Four months later anterior pituitary extract from sheep was given for five months, during which time she had three menses with nonsecretory endometrium. Treatment was discontinued. In the next six months no menses occurred. The pregnant mare's serum hormone was followed by menses and occasional secretory endometrium. Anterior pituitary extract was followed by menses but no secretory effect.

CASE 12.—The patient began menstruating for the first time in thirteen months after one series of gonadogen. Injections were continued each month for twelve months. Biopsies taken each month before the menses showed secretory endometrium twice and nonsecretory nine times. Once there was slight endometrial hyperplasia. The injections were changed to synapoidin each month for seven months. Secretory endometrium occurred twice and nonsecretory five times. In this case, synapoidin (a mixture of chorionic gonadotropin and anterior pituitary extract) seemed to give the same secretory effects as the pregnant mare's serum hormone.

TABLE II. ENDOMETRIAL HYPERPLASIA WITH METRORRHAGIA

CASE	AGE	DURATION	P.M.S. UNITS	OBSERVED	RESULT	FOLLOW-UP BIOPSY
1	20	4 yr.	200	6 mo.	Regular menses 6 mo. Recurrence	Hyperplasia
2	25	8 yr.	260	16 mo.	Not improved	Hyperplasia
3	23	2 yr.	350	6 mo.	Not improved	Hyperplasia
4	18	5 yr.	140	2 mo.	Not improved	Hyperplasia
5	25	4 mo.	90	1 mo.		Hyperplasia
6	43	2 yr.	120	6 mo.	Not improved	Secretory
7	23	5 yr.	120	12 mo.	Improved 8 mo. Recurrence	Hyperplasia
8	28	10 yr.	180	30 mo.	Temp. improved	Hyperplasia

METRORRHAGIA

Eight patients with metrorrhagia and proved endometrial hyperplasia with "Swiss cheese" glands and nonsecretory epithelium have been treated with pregnant mare's serum hormone. The total dosage has varied from 90 to 350 units. Four patients were not improved in any degree. Three had fairly regular normal menses for six to twelve months, after which there was recurrence of the metrorrhagia. The recurrence was helped in 2 cases, while one recurred a third time when the bleeding did not stop after the hormone. Follow-up biopsies showed no change in the hyperplastic endometrium in 7 cases. One patient, aged 43 years, did show a premenstrual endometrium on two occasions after the hormone was given. This patient was found at operation to have a small submucous myoma. The results in these 8 cases were not very encouraging for the treatment of endometrial hyperplasia.

Ten other patients with metrorrhagia have had endometrial biopsies which failed to show hyperplasia. Three had secretory endometrium before, during, and after treatment, but the metrorrhagia continued without improvement. Seven patients showed interval nonsecretory endometrium before treatment. Three had regular menses; the patients were followed for from six to fourteen months. One of these remained anovulatory, the second showed early secretion in one cycle and no secretion in three cycles, while the third had normal premenstrual endometrium on two occasions. Three patients remained unimproved as far as regulating the bleeding was concerned, but during treatment 2 showed early secretory endometrium.

TABLE III. METRORRHAGIA WITH BIOPSY

CASE	AGE	BIOPSY	TREATMENT UNITS P.M.S.	OBSERVATION	RESULT	BIOPSY AFTER TREATMENT
1	20	Premenst.	250	3 mo.	Not imp.	Same
2	29	Premenst.	60	4 mo.	Not imp.	Same
3	29	Slight secretion	330	6 mo.	Not imp.	Slight secretion
4	18	Nonsecretory	60	6 mo.	Regular	Nonsecretory
5	16	Nonsecretory	200	6 mo.	Imp.	Slight secretion
6	22	Nonsecretory	30	14 mo.	Regular	Secretory
7	18	Nonsecretory	140	8 mo.	Not imp.	Slight secretion
8	15	Nonsecretory	60			
9	29	Nonsecretory	150	12 mo.	Not imp.	Slight secretion
10	22	Nonsecretory	60	9 mo.	Not imp.	

Only 3 out of 10 patients were clinically relieved of the metrorrhagia. Four of 7 patients with anovulatory endometrium showed some degree of secretion in the endometrium during treatment. This would suggest that some response was obtained in the ovary and that the treatment may have been incomplete. As yet the treatment of metrorrhagia has not been simplified.

Nine additional cases of metrorrhagia have been treated without biopsies. Five had puberty metrorrhagia; the ages of the patients varied from 9 to 15 years. At least very good temporary results have been obtained in 4 cases, although one patient has had a recurrence after eight months. One of these girls developed a temporary painful cystic ovary during treatment. The other four patients had only slight bleeding between periods. Three seemed to be improved and one showed no improvement.

A study of these 27 cases of metrorrhagia suggests that the pregnant mare's serum hormone is of value in about one-half of the cases. Possibly one-half of the cases might improve anyway. The finding of secretory effects in 5 anovulatory bleeding cases does suggest that ovarian stimulation has taken place. The series of puberty metrorrhagia is too small for conclusions, but does suggest the possible use of pregnant mare's serum hormone in these cases.

TABLE IV. METRORRHAGIA WITHOUT BIOPSY

CASE	AGE	DURATION	TREATMENT UNITS P.M.S.	OBSERVATION	RESULT
1	13	4 mo.	70		
2	9	7 mo.	60	9 mo.	Normal 8 mo. Recurrence
3	14	3 mo.	60	3 mo.	Normal. Cystic ovary
4	15	3 mo.	60	3 mo.	Normal
5	14	6 mo.	240	5 mo.	Normal
6	26	6 mo.	60	1 mo.	Improved
7	32	5 mo.	120	3 mo.	Not improved
8	25	1 mo.	30	6 mo.	Normal
9	29	2 mo.	60	6 mo.	Improved

DYSMENORRHEA

The treatment of dysmenorrhea is one of the most difficult problems in gynecology. Innumerable remedies have been offered. The whole matter is so confusing and unsatisfactory that one feels there is no dependable therapy.

Dysmenorrhea may be readily classified into two types, the secondary or extrinsic type and the primary or intrinsic type. The secondary group includes those due to definite cervical strictures, intramural or submucous myomas of the uterus, chronic salpingitis with menstrual exacerbations, and various pelvic tumors. An exceedingly important and common cause is endometriosis, with either adenomyomas of the uterus or implants in the abdominal cavity. Endometriosis may be suspected when an ovary is adherent and more readily diagnosed when there are palpable densely adherent cysts or nodules and induration in the rectovaginal septum. On the other hand, the preoperative diagnosis may be impossible because of the small size of the implants. Some

TABLE V. DYSMENORRHEA

CASE	AGE	RACE	BIOPSY BEFORE TREATMENT	TREATMENT UNITS PER MONTH	BIOPSY AFTER TREATMENT	OBSERVATION	IMPROVEMENT	REMARKS
1	20	C	Premenst.	60-30-60-60-50-60	Premenst. 1×	16 mo.	Moderate	Pregnant 10 mo. later
2	15	C	Premenst.	30-60-60-60	Premenst. 4×	21 mo.	Marked	
3	19	C	Premenst.	60-60-60-60-60-60-60	Premenst. 4×	23 mo.	Slight	Operation old ruptured appendix
4	22	C	Premenst.	50-60-60-60-60-50	Premenst. 2×	23 mo.	Marked	
5	14	C	Early secret.	60-10		2 mo.	None	Later active tuberculous lungs and salpingitis
6	17	C	Premenst. 3×	60		4 mo.	Slight	Pregnant after 4 mo.
7	17	W		60-60	Nonsecret. 3×	15 mo.	Marked	
8	21	W	Premenst.	60-30-30-30-60-60-60	Premenst. 6×	8 mo.	None	Operation: endometriosis
9	16	W		60-100-40-50		9 mo.	Moderate	
10	21	W		60-60-60-60		12 mo.	Moderate	Temporary cyst after fourth series
11	24	W		60-60-60		16 mo.	None	Marked anteflexion
12	21	W		60-60-60		9 mo.	Slight	Pregnant 6 mo. later
13	21	W		60-60-60-60		10 mo.	None	Adherent ovary: ?endometriosis
14	23	W		70-60		3 mo.	Worse	Operation: endometriosis
15	28	W		60-60-60-60 60-60-60-60 60-60		18 mo.	Marked	
16	30	W		60-60		8 mo.	Moderate	
17	20	W		750-1000-1000 (Anteron)-60-60		11 mo.	None	Marked anteflexion
18	23	W		60-60-60-60		18 mo.	Marked	
19	30	W		60-60-60-60 60-60-30		12 mo.	Marked	Cystic ovary 2× Pregnant
20	17	W		60-60		7 mo.	Marked	
21	30	W		750 (Anteron)		9 mo.	None	Cure after stem pessary
22	27	W		60		7 mo.	None	Local reactions. Adherent ovary: ?endometriosis
23	21	W		60-60-60-60-60		8 mo.	Marked	
24	19	W		60-60-60-60		4 mo.	Marked	
25	24	W		60-60-60		10 mo.	Moderate	
26	21	W		60		8 mo.	Slight	
27	22	W		60-60		3 mo.	Moderate	
28	24	W		60-60-60		8 mo.	Moderate	
29	21	W		60-60-60-60		10 mo.	None	Anteflexion. Stem pessary with relief
30	13	W		30-30		2 mo.	Marked	

intractable cases with supposedly primary dysmenorrhea are actually due to endometriosis. Recurrent menstrual appendicitis may be a factor in some cases. The pain may be caused by ureteral obstruction in the form of spasm or stricture.

Primary dysmenorrhea is applied to those cases in which no pathology can be demonstrated, other than variations in size and angulation. There is difference of opinion as to whether angulation and the small canal constitute sufficient etiology to place these cases in the secondary group. Most authors consider them primary, feeling that the etiology is of developmental or endocrine origin.

In the majority of patients with primary dysmenorrhea, the history includes the usual menarche at about fourteen years with painless supposedly anovulatory menses for some two years. During this time, the uterus is of the small juvenile type. At sixteen years of age, cramps appear, apparently associated with beginning ovulation. From eighteen to twenty years of age the pain is often very severe and the uterus is usually adolescent in type, being perhaps of normal length but quite narrow. Between the ages of 22 and 25, the pain diminishes to a mild, undisturbing cramping, and the body of the uterus particularly is found quite well developed. There are, of course, exceptions to this sequence, but it is the commonest that we have seen.

Psychiatric factors, thyroid, iodine, malnutrition, lack of exercise, and systemic disease have been brought out as important in treatment.

Endocrine influences are incompletely understood. The estrogenic hormones directly regulate the size of the uterus in proportion to the amount of hormone present, unless the uterus as a receptor has some degree of insensitivity. Treatment has been directed to developing the uterus by additional estrogens parenterally. Sturgis and Albright[7] have found that the subsequent period will be painless if large doses of estrogens, which prevent ovulation, are given early in the cycle. Although not too encouraging, it does seem that estrogens over a long period of time may have a lasting effect in relieving dysmenorrhea in some cases.

Progesterone is of value in certain cases when the uterus is well developed, and prolonged relief may follow therapy given over a few months. Testosterone seems effective by depressing the pituitary and ovary and preventing ovulation, but probably gives no lasting cure. Chorionic gonadotropin is of questionable value in the treatment of any woman.

In a previous paper (Gray and Manly, 1940) the pregnant mare's serum hormone seemed of value in the treatment of patients with dysmenorrhea. A longer follow-up of the earlier cases and other new cases are here reported.

Thirty women have been treated with the pregnant mare's serum hormone for supposedly primary dysmenorrhea. Only patients with marked pain are included. The age varied from 13 to 30, averaging twenty-one years. Twenty-four were white and 6 were colored.

One or more endometrial biopsies were taken immediately before menstruation and preceding treatment in 7 cases. Six showed premenstrual secretory endometrium and one showed questionable early secretion. The following month the latter case was found to have active pulmonary tuberculosis and apparently acute salpingitis. Biopsies were taken during and after treatment in 7 cases, showing normal premen-

strual endometrium in six. One patient (Case 7) had 3 biopsies taken after treatment which showed nonsecretory endometrium. These 3 menses were entirely painless, but several other periods were associated with slight cramps and may have been ovulatory cycles. The evidence in the other 6 cases indicates that the ovaries were ovulating when severe pain was present and that treatment did not interfere with ovulation.

Nine patients in this series had practically complete relief of menstrual pain. Eight had moderate relief, being much improved. Four had only slight relief. Two of the latter were treated only one month, and a third one at exploratory operation had an old ruptured appendix.

Nine patients in this series had no relief from treatment. Two (Cases 21 and 29) had stem pessaries with subsequent relief, and two (Cases 11 and 17) had very small uteri with marked acute anteflexion. The latter we believe should have stem pessaries. Two (Cases 8 and 14) had exploratory operations with findings of numerous minute endometrial implants. In each of two patients (Cases 13 and 22), there was a slightly adherent ovary, and the patients have been advised to have exploration for possible endometriosis. Tuberculosis was discovered in the ninth patient (Case 5) after one month's treatment, and treatment was discontinued.

The general impression of efficacious therapy has been obtained in this study. It has seemed that the uteri in most cases have developed rapidly from the adolescent to more adult size. In some there has been varying regression in size after discontinuing therapy, with largely maintenance of improvement. Evidently certain of the failures were actually secondary dysmenorrheas. During treatment, two patients developed painful cysts which regressed in the subsequent cycle. Four patients became pregnant shortly after treatment, one (Case 19) having complained of sterility for six years.

MALE STERILITY

Previous to the past eighteen months our work in sterility included only the most cursory studies of the male. Huehner tests and direct microscopic examinations of condom specimens often give entirely false impressions. The former may show the effect of female secretions, but nothing regarding the number of spermatozoa. Either the rubber or powder in condoms so alters the viability and count as to make observations undependable, as reported in recent literature. Therefore, we made sperm analyses from masturbated specimens, including gross appearance, volume, liquefaction time, pH, motility, total count, and differential count of stained smears. While these many points are important in evaluating the fertility of a man, it seems that the total count per cubic centimeter is the most important determination, as the other characteristics generally follow variations in the count. As stated in the literature by Hotchkiss[8] (1936) and others, 60 millions per c.c. seems to be the lower limit of normal, relative sterility being below this number, approaching absolute sterility of zero.

In the past, hormone therapy for sterility in men has been very discouraging. Looney[9] (1940) reported a single case thoroughly studied and treated with pregnant mare's serum hormone. In that case the sperm count rose from 32 millions to 133 millions. Conception could not occur because the wife had nonpatent tubes. Heckel[10] (1940) re-

TABLE VI. STERILITY IN MEN

CASE	AGE	MILLIONS PER C.C. BEFORE TREATMENT	TREATMENT UNITS P.M.S.	MILLIONS DURING TREATMENT	FINAL COUNT
1	45	1.2	550	6.5	3.1
2	39	35.0	140		
3	33	22.5	290	35.0	180.0
				117.0	
4	30	0.6	400	15.0	51.8
5	36	32.0	200	57.5	Normal pregnancy. Count 15 mo. later 374
6	32	30.8	300		415.8
7	32	22.5	360	19.6	
				35.6	Pregnancy, miscarriage
				67.9	
8	48	5.0	120		5.0
9	30	Small number	750 A.P.E.*		Normal pregnancy
		2.5	120 P.M.S.*	12.5	
			740 A.P.E.	1.6	
			200 P.M.S.	2.5	
				0.4	0.4
10	34	29.5	200		
11	28	42.8	Thyroid	64.9	76.6
12	30	6.2	Thyroid	36.2	
				67.2	4.5
13	27	None	Thyroid	One sperm	
14	52	1.8	None		
15	49	2.5	None		
16	34	7.5	None. Active tuberculosis		
17	37	None	None		
18	30	None	None		

*A.P.E., anterior pituitary extract; P.M.S., pregnant mare's serum.

ported a single case with increase in count from about 50 millions to 219 millions with this hormone. After nine months without treatment the count was 56 millions. Charny[11] (1940) reported 5 patients treated with the pregnant mare's serum hormone. Three showed definite improvement in the count although in none had the count increased to normal.

The husbands of 45 private patients complaining of sterility have had sperm analyses from masturbated specimens. Eighteen (40 per cent) of these men had sperm counts below 60 millions per c.c., considered an important factor in the sterility of these couples. Fifteen (33 per cent) were considered relatively sterile and three (7 per cent) absolutely sterile.

Of the 15 relatively sterile men, two were not encouraged to take treatment because of their age (49 and 52 years). One was not treated specifically, because his routine physical examination revealed unsuspected active pulmonary tuberculosis. Of the remaining, two with hypothyroidism showed increase to normal counts with thyroid alone, although one was a little irregular in taking the thyroid, and the count fell to 4.5 millions in six months.

Ten men have been treated with the pregnant mare's serum hormone for relative sterility. Four had previously taken thyroid, apparently without effect. Very definite increases in the count occurred in five after the use of gonadogen. In one (Case 5), there followed a full-term normal pregnancy (two miscarriages had occurred five and six years earlier). In another instance (Case 7), there was a pregnancy ending

in miscarriage. Two patients (aged 45 and 48) showed no improvement whatever. A third patient without improvement (Case 9) was most interesting. Three years ago this man, aged 27 years, had a very small number of sluggishly motile sperm. (At that time sperm counts were not being made by us.) Fifteen injections of sheep's anterior pituitary extract were given; there followed a full-term normal pregnancy. Six months ago he returned because of sterility. The count showed 2.5 millions. All treatment has been unavailing in further sperm stimulation, including a series of pregnant mare's serum hormone, a series of sheep's anterior pituitary extract, and a second series of pregnant mare's serum hormone. The basal metabolism was normal. At present, for the first time, he is receiving thyroid to tolerance. After one month there has been no improvement. In the two remaining cases counts have not been obtained after treatment.

In this series the dosage was usually 10 units three times weekly, although some received 20 units three times weekly. Total dosages of 200 to 550 units were employed. It is possible that in some cases far larger amounts should have been given. One patient (Case 8) had local reactions, but continued for twelve injections.

Our records apparently have indicated stimulating effects in five men from the pregnant mare's serum hormone and failures in three cases. Two failures were in individuals 45 and 48 years old, the oldest in the series, and one of these had recurrent chronic osteomyelitis. One other failure was in a young man who seemingly responded three years earlier to anterior pituitary extract.

SUMMARY

1. The effect of the pregnant mare's serum hormone in the form of "gonadogen" has been studied in 83 cases in the past three years.

2. In 16 patients with secondary amenorrhea, treated from one to nineteen months, 12 menstruated and 2 were refractory after nine and twelve months of continuous treatment. In the 12 who had cyclic menstruation under treatment, 6 showed a secretory and 4 a nonsecretory endometrium. In these 6 cases, 12 cycles were secretory and 24 anovulatory. One case was followed immediately after one secretory biopsy by normal pregnancy.

3. In 8 patients with endometrial hyperplasia, 4 showed some clinical improvement, although 3 relapsed. The endometrial hyperplasia remained the same in 7, while one developed premenstrual endometrium.

4. In nineteen other patients with metrorrhagia, 10 showed clinical improvement, although somewhat equivocal. Four of 7 patients with anovulatory endometrium had varying degree of secretion in the endometrium during treatment. This suggests some active effect from the hormone.

5. In 30 patients with supposedly primary dysmenorrhea, 21 were improved (9 marked, 8 moderate, 4 slight). Of the 9 failures, secondary factors entered practically every case. Four patients became pregnant during or shortly after treatment.

6. Temporary painful cysts of the ovary occurred in 5 women: they disappeared with the following cycle. Further treatment was accompanied by recurrence of the cyst in one case.

7. In 10 men with relative sterility, 5 were improved and 3 remained unimproved. One full-term normal pregnancy and one miscarriage were obtained in these couples.

8. No serious sensitivity reactions occurred in any case.

The equine gonadotropin used in these cases was entirely in the form of gonadogen, very generously supplied by the Upjohn Company, except in two cases where anteron was used, supplied by the Schering Corporation. The anterior pituitary extract mentioned in follow-up studies of certain patients with amenorrhea was furnished by the Winthrop Chemical Company. Synapoidin was supplied by Parke, Davis and Company.

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DISCUSSION

DR. EUGENE H. COUNTISS, New Orleans, La.—It would be interesting if Dr. Gray would tell us something of the change in the ovaries in these cases with manipulation and curettage. Were small follicular cysts ruptured, thus allowing a more normal corpus luteum factor?

We now know that a disturbance of gonadotropic function is not the same in primary as in secondary amenorrhea, and that excessive production of gonadotropic hormone could be the cause of secondary amenorrhea.

Dr. Gray would lead us to believe that in cases of menorrhagia, pregnant mare's serum is not of much value. Hyperhormonal bleeding is due to disturbed gonadotropic secretion in the anterior pituitary, and male sex hormone acts by directly inhibiting gonadotropic secretion of the anterior pituitary. In the cases of endometrial hyperplasia, 50 per cent gave failures, while 4 were enough improved to encourage treatment with pregnant mare's serum. They all became refractory later and returned to the nonsecretory state.

In the 30 patients with dysmenorrhea treated with pregnant mare's serum, relief was obtained often enough to warrant further trial.

In managing male sterility, I would like to stress the importance of the masturbated specimens, as these alone offer a true evaluation.

DR. L. W. MASON, Denver, Colo.—One has to be extremely careful in clinical evaluation when giving hormone preparations to a woman whose machinery, may I say, is intact. Whenever I feel my feet getting off the ground in enthusiasm at results which I seem to be obtaining by treatment, I think of the 16 cases of amenorrhea that Dr. R. G. Gustavson of the Department of Chemistry at the University of Colorado and I were studying several years ago from the standpoint of estrin

determinations. Before we could complete the study, 5 of the individuals had menstruated spontaneously.

One would think that the ideal indication for the pregnant mare's serum would be those cases in which the only abnormality found was a deficient menstrual endometrium. I have two slides each from three sterility cases which were thoroughly studied, and which fall into that group.

1. The first slide is one of several biopsies taken at the beginning of menstruation, none of which showed any evidence of ovulation. The patient was given three intramuscular injections of gonadin in 200 unit doses three times a week, and 600 units just before the time of expected ovulation. This was repeated over several months, with increasing dosages. The next slide of this case, taken three months after beginning treatment, shows, I think, some improvement in the endometrium, which, however, is still markedly deficient in secretory activity. Whether this improvement is spontaneous or resulted from the treatment, I do not know.

2. The slide from the second case, before treatment, shows evidence of ovulation, because there are secretory changes in the glands, but you will all agree that it is far from normal. This patient was given various combinations of dosages at various times during the next several months. The second slide of this case, taken several months after beginning treatment, shows an endometrial picture which is inferior to the first one, before treatment was instituted. Was this spontaneous, or the result of treatment?

3. The first slide from the third case shows definite evidence of ovulation, but it shows, I consider, a deficiency in secretory activity. This patient was given large doses of pregnant mare's serum (2,000 units) at various times through a period of several months. The second slide, after two months' treatment, shows what appears to be a characteristic cystic glandular hyperplasia. This was in a woman in her early twenties, whose menstrual history had always been essentially normal. This change may be spontaneous, but it may also be due to the very large doses of the serum. It may be that in such dosages, the material may stimulate multiple follicle formation, without normal evolution and corpus luteum formation, so that we get the picture we see in the typical menopausal cystic hyperplasia.

In none of these cases did pregnancy occur, and Mazer and Israel, in their new book, find its use disappointing in the treatment of sterility. I think this last slide will show the wisdom of keeping before our minds the motto which appears in the delivery rooms at the Chicago Lying-in Hospital: Primum Non Nocere—first do no harm. These newer hormone preparations are potent, and if they do not always do what we want them to do, they doubtless do something.

DR. KARL JOHN KARNAKY, HOUSTON, TEXAS.—Our results with pregnant mare's serum at the Jefferson Davis Hospital have been such that we do not advocate its use in women. For a study of the effects of this substance we selected a group of approximately 10 women who gave a history of normal menstruation. An endometrial biopsy was taken on these women on the first day of their menstruation and all the endometriums were premenstrual. Some individuals were given 1,000 international units, some 3,000 international units, some 6,000 international units, some 12,000 international units of pregnant mare's serum, every day or every other day or once a week, for approximately nine months. Endometrial biopsies were taken every month and in some cases every other month. In not one case did the menstrual cycle change from that previously recorded, which was normal at the beginning of treatment. All of the endometrial biopsies taken on the first day of menstruation still showed premenstrual endometrium. Pregnant mare's serum should have stimulated these normal ovaries so much that an irregularity of the menses should be produced. In view of this failure what can we expect pregnant mare's serum to do to abnormal ovaries?

If we gave synapoidin, a combination of A. P. L. and pituitary synergist, we obtained a definite upset in the menstrual rhythm. Synapoidin apparently will replace pregnant mare's serum.

DR. GRAY (closing).—Much of the accurate work with negative results has followed the use of a commercial preparation marketed in solution. Such solutions may be unstable. Results should be interpreted in the light of whether the dried product or prepared solution is used.

GYNECOGRAPHIC AID IN THE DIAGNOSIS OF ECTOPIC PREGNANCY*

IRVING F. STEIN, M.D., CHICAGO, ILL.

(From the Michael Reese Hospital and Northwestern University Medical School)

IT IS well recognized by the medical profession that ectopic pregnancy presents a confusing and decidedly inconsistent clinical picture. This is entirely comprehensible if we consider four conditioning factors, namely: (1) the variety of extrauterine locations; (2) preexisting pathologic conditions of these sites; (3) the duration of extrauterine pregnancy in a given site; and (4) occasional re-implantation of the ovum in another situation. The various types of implantation in the Fallopian tube, intramural, isthmic, ampullar and fimbrial, may give rise to differing syndromes, and the ovarian, abdominal, and cervical pregnancies create dissimilar symptoms. Previous inflammatory tubal disease and functional ovarian swellings often present elements which add to the confusion. Both the location and the duration of ectopic implantation are significant in relation to the severity of attack, the amount of hemorrhage, and to some extent, the prognosis.

The symptoms at onset are commonly those which are typical for normal intrauterine pregnancy, but in some cases, these are entirely lacking and the first intimation of the existence of pregnancy may be the sudden occurrence of severe pain, shock, and signs of intraperitoneal hemorrhage.

The diagnosis of ectopic pregnancy depends chiefly upon a carefully considered history and the findings on bimanual examination, but that there is no *reliable* typical history is well recognized; in some cases, even the most usual symptoms may be lacking. Upon examination, furthermore, in early cases there is often *no palpable swelling* or mass to be found, so that the diagnosis rests chiefly upon exceptional tenderness of the affected side.

Because of the protean nature of this disorder and the frequency with which it fails to follow a typical pattern, many diagnostic aids to facili-

*Presented, by title, at the Thirteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, New Orleans, La., October 2 to 4, 1941.

tate recognition of ectopic pregnancy have been described. It is especially in those cases in which the diagnosis is obscure, the differential difficult, and a decision urgent, that diagnostic aids other than those ordinarily employed are indicated. The prime object in utilizing additional aids is to decide upon prompt surgical intervention when the diagnosis of ectopic pregnancy is thereby established, and also to avoid laparotomy in cases simulating the picture of ectopic pregnancy but in which operation should not be performed. Many careful surgeons and gynecologists have operated for tubal pregnancy only to be embarrassed to find that both Fallopian tubes were normal and the pregnancy was intrauterine. Subsequent inquiry sometimes reveals that the patient herself produced the misleading symptoms by the ingestion of oxytocic drugs intended as abortefacients; furthermore, that the facts were purposely withheld from the physician in the hope of getting rid of an undesired pregnancy. Willful deception as well as inaccurate recital of symptoms must be taken into consideration in obtaining a history.

Whenever the usual symptoms of early pregnancy, such as delayed menses, breast fullness, nausea, and urinary frequency, are followed by irregular but slight bleeding and some colicky pains, the presence of tubal pregnancy should be considered likely. When, in addition, acute adnexal tenderness is found, the diagnosis is more certain. If a definite, soft, and very tender mass is palpable, the diagnosis is practically assured. However, inasmuch as many other pelvic conditions may produce symptoms and signs quite similar to those of ectopic pregnancy, a careful differential diagnosis must be made. Conditions mainly to be ruled out are: intrauterine pregnancy with or without threatened abortion; chronic salpingitis, hematosalpinx; cysts of the ovary, especially the corpus luteum cyst; torsion of the ovary or adnexa; acute appendicitis; retroflexed gravid uterus; intraperitoneal bleeding from a ruptured follicle or corpus luteum cyst.

The unruptured, early ectopic pregnancy presents the chief diagnostic problem, for after tubal rupture the picture changes so characteristically that the diagnosis is usually simplified. In this communication relating to the use of gynecography, only the diagnosis of unruptured ectopic pregnancy and tubal mole will be considered. Radiographic methods of diagnosis have been described by others, chiefly for cases of advanced ectopic pregnancy, especially abdominal pregnancy. In such cases, the fetal skeleton has been demonstrated outside the uterus, and the uterine cavity visualized by a sound or by means of the instillation of opaque media.[1] The identification of a small, empty uterine cavity by such means serves as conclusive evidence in abdominal pregnancy.[2] Snow[3] has shown in addition that by soft tissue x-rays, the placenta, uterine wall, and amniotic sac can be demonstrated. The lack of uterine wall shadow over the fetus, he believes, is an important clew in the diagnosis of abdominal pregnancy.

In order to establish a diagnosis of ectopic pregnancy, the diagnosis of an existing pregnancy must first be made, and then a decision as to whether the pregnancy is intra- or extrauterine. In any case presenting the usual symptoms of early pregnancy in which spotting or early bleeding occurs, and especially if there is also some pelvic pain, extrauterine pregnancy must be considered likely. Irregular bleeding, usually slight, occurs in about three-fourths of the cases, and pain is characteristic of from 80 to 96 per cent of cases. It is rare to be able to palpate the very early unruptured tubal pregnancy; however, the discovery of a highly sensitive tube has great significance in suspicious cases.

Some of the signs and tests which may be of value for differential diagnosis become useful only after a certain amount of intraperitoneal bleeding has occurred, such as Cullen's "black umbilicus" (rarely observed), and blood obtained by cul-de-sac puncture. The Friedman test is usually positive in about half of the cases of ectopic pregnancies: Those in which the fetus is alive and/or chorionic tissue is proliferating. The drawback to its use is the forty-eight-hour delay. Perhaps the Falls' colostrum skin test will prove reliable as a substitute after more extensive trial. The advantage of the Falls' test is that the reaction appears within one hour. Both of these tests, however, may prove positive in the presence of a corpus luteum cyst, one of the chief conditions to be differentiated, and therefore cannot be considered conclusive. A positive pregnancy test usually implies a living ovum or at least, growing chorionic tissue; then the question of the intra- or extrauterine site must be decided. Blood counts are of little value early, for it is only when intraperitoneal bleeding occurs that the white blood count is increased, and the sedimentation rate remains normal until considerable hemorrhage and anemia occurs. These tests do not indicate the state of the ovum in the tube or the presence or absence of decidua.

The value of diagnostic curettage has been a matter of considerable controversy. When a definite decidua and complete absence of chorionic villi is found upon curettage, the diagnosis of extrauterine pregnancy is supported, but according to Novak,[4] in only about one-half the cases is decidua found.

Heaney[5] makes the point that a "dry scrape," in which no tissue is obtained, in a suspect case is almost certain evidence of ectopic pregnancy. He states that the fewer the scrapings, the more probable the presence of ectopic gestation, as most patients expel the decidual cast before coming to operation. Siddall and Jarvis[6] state that while the findings of decidua without villi is strong presumptive evidence of extrauterine pregnancy, the absence of decidua is not reliable evidence against its presence. Rock,[7] on the other hand, is of the opinion that curettage for the recovery of decidua without villi is rarely if ever desirable. It is in the cases in which the Aschheim-Zondek or Friedman tests are negative that there is usually no decidua in the uterus. Goldblatt and Schwartz[8] found that there was a close but not perfect relationship be-

tween the state of preservation of the chorionic tissue and the Friedman test, and the latter was not always directly related to the presence of decidua. The presence of decidual reaction in the uterus depends, they believe, upon the duration and amount of uterine bleeding. They agreed with Siddall and Jarvis that patients with ectopic pregnancy who bleed scantily may show uterine decidua but with decreased expectancy as the duration of bleeding increases; those patients who bleed moderately or profusely for more than three weeks are extremely unlikely to have a uterine decidua.

Biopsy specimens of decidua may be obtained in suspected cases by means of the suction curette, but if intrauterine pregnancy has not been definitely ruled out, this should not be attempted. This advice appears sound in spite of Sturgis' report[9] of 7 endometrial biopsies in intrauterine pregnancy without harmful results. It must be borne in mind, moreover, that decidua-like changes may occur in the absence of pregnancy due to progesterone effects[10] and that there is no characteristic endometrial picture in ectopic pregnancy.

Cul-de-sac puncture has been accepted as a means of determining the presence of blood in the peritoneal cavity. It has no value, however, in cases of unruptured ectopic with the exception of cases of partial tubal abortion. Posterior colpotomy, however, is advocated as a diagnostic procedure by a number of authorities. Torpin[11] believes it should be done in every case where the diagnosis is uncertain, and Heaney[5] prefers it to simple puncture, believing that the danger from the procedure is slight. Furthermore, if the pregnant tube is accessible, it may be removed through the colpotomy opening.

Peritoneoscopy has also been used successfully by Ruddock,[12] Hope,[13] and others, but the method has not received general acceptance.

For the diagnosis of early and especially unruptured ectopic pregnancy, and for tubal mole, two methods of x-ray are available which may be grouped under the term "gynecography." One of these, hysterosalpingography, is dependent upon the use of an opaque substance, while the other employs a gaseous medium to produce pneumoperitoneum; i.e., pneumoroentgenography. The two methods may be used independently or combined with each other. By means of a contrast medium, the uterine cavity may be demonstrated on the x-ray film, as well as tubal lumen, when the tubes are open. In intrauterine pregnancy, the uterus is distensible and usually shows the imprint of the ovum in an enlarged cavity. In extrauterine pregnancy, the uterine cavity will usually be shown as normal in size, triangular or oval, but without the imprint. The tubes may or may not be patent, for if decidua fills the uterine ostia of the tubes, no contrast medium will pass. On the other hand, if the uterine decidua has been shed, both tubes may admit the medium, provided that they are not otherwise blocked by the pregnancy or by previous inflammatory damage.

Bortini[14] reports that the diagnosis of early extrauterine pregnancy can be made by hysterosalpingography, the uterine shadow appearing triangular or slightly round, and the uterus slightly deviated to the affected side. If the ampulla is the site of tubal pregnancy, the opaque medium shows a characteristic distribution through this segment. Mathieu[15] claimed that by hysterosalpingography a diagnosis of early tubal pregnancy could always be made (100 per cent!), and that in tubal abortion the mass can be visualized, the oil surrounding the mass rendering it radiopaque. Furthermore, he stated that when pregnancy was in the midportion of the tube, a rounded shadow appeared at the stopping point of the opaque medium; this he considered to be pathognomonic of tubal pregnancy. I have failed to observe this sign in my cases.

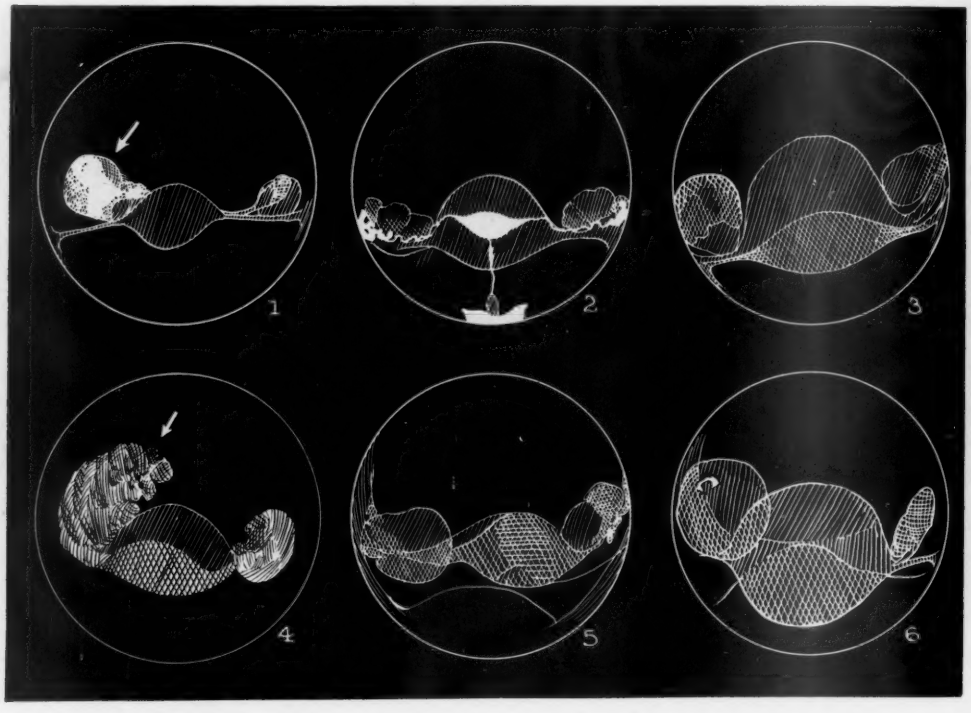

Fig. 1.—Differential diagnosis of ectopic pregnancy with gynecography. *1*, Unruptured tubal pregnancy (transabdominal pneumoperitoneum); *2*, normal uterus, ovaries and tubes (combined gynecography); *3*, intrauterine pregnancy, 6 weeks (transabdominal pneumoperitoneum). Cases 4, 5, 6: Similar symptoms: Delayed menses, colicky pain, spotting. Similar findings: Tender mass on right side. *4*, Unruptured right tubal pregnancy, blood in fimbriated end; *5*, right lutein cyst; *6*, pregnancy, 6 weeks; complicated by right twisted dermoid. (Note area of calcification.)

Pneumoroentgenography is no new procedure in gynecology. I[16] have reported periodically the results obtained at Michael Reese Hospital and described the technique fully. I have employed the method in selected cases for almost two decades, particularly in cases of sterility and for gynecologic differential diagnosis. I first reported a case of tubal pregnancy diagnosed by pneumoroentgenography in 1926.* Its use in

*Surg., Gynec. & Obst. 42: 83, 1926.

ectopic pregnancy has been limited to cases of unruptured tubal pregnancy and the pelvic lesions which compete with it in diagnosis, and also cases of missed ectopic pregnancy which result in tubal mole. The method is not recommended for the acutely ill patient with shock or intraperitoneal hemorrhage.

Not infrequently, patients who have been under observation and treatment for sterility present symptoms suggestive of ectopic pregnancy. The bimanual findings often prove vague in such cases, and the Friedman test may be negative. Diagnostic curettage or even an endometrial

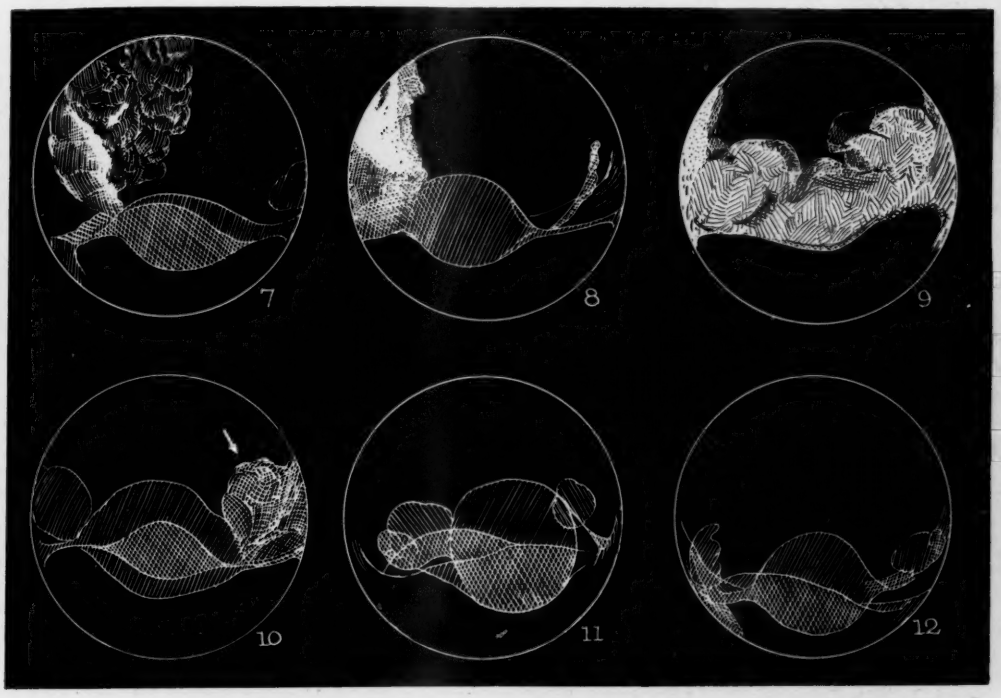

Fig. 2.—7, Right unruptured tubal pregnancy: Bleeding from fimbriated end; 8, unilateral inflammatory disease right adnexa: simulating picture of ectopic pregnancy; 9, bilateral inflammatory: Symptoms suggestive of ectopic pregnancy. Cases 10, 11, 12: Similar symptoms: Irregular or delayed menses, pelvic pain, tenderness. *10*, Left tubal pregnancy: unruptured; *11*, intrauterine pregnancy, 6 weeks: right ovary globular, tender; *12*, normal pelvic viscera; sterility.

biopsy under such circumstances would be inadvisable unless intrauterine pregnancy were ruled out with certainty. Furthermore, even hysterosalpingography is not to be recommended, for, as I have consistently warned, all intrauterine instrumentation is contraindicated in a patient with suspected pregnancy, intra- or extrauterine. On the other hand, *transabdominal pneumoroentgenography* may be used without danger of disturbing a pregnancy. There are no contraindications to the use of this method in unruptured ectopic or intrauterine pregnancy. When a satisfactory film is obtained after pneumoperitoneum is induced, the patient being radiographed in the characteristic partial

knee-chest posture, a replica of the pelvic status appears in the film (Fig. 1). The uterus, tubes, and ovaries can be differentiated sufficiently to recognize tubal involvement. Ovarian cysts are easily ruled out as they appear as smooth, round structures separate from the tubes. Tubal pregnancy often appears as a dense, cone-shaped shadow, the apex arising from the uterine horn. The size depends upon the duration of the pregnancy. The ovary on the same side may be seen as a separate oval structure or may form part of the adnexal mass. In contrast, the

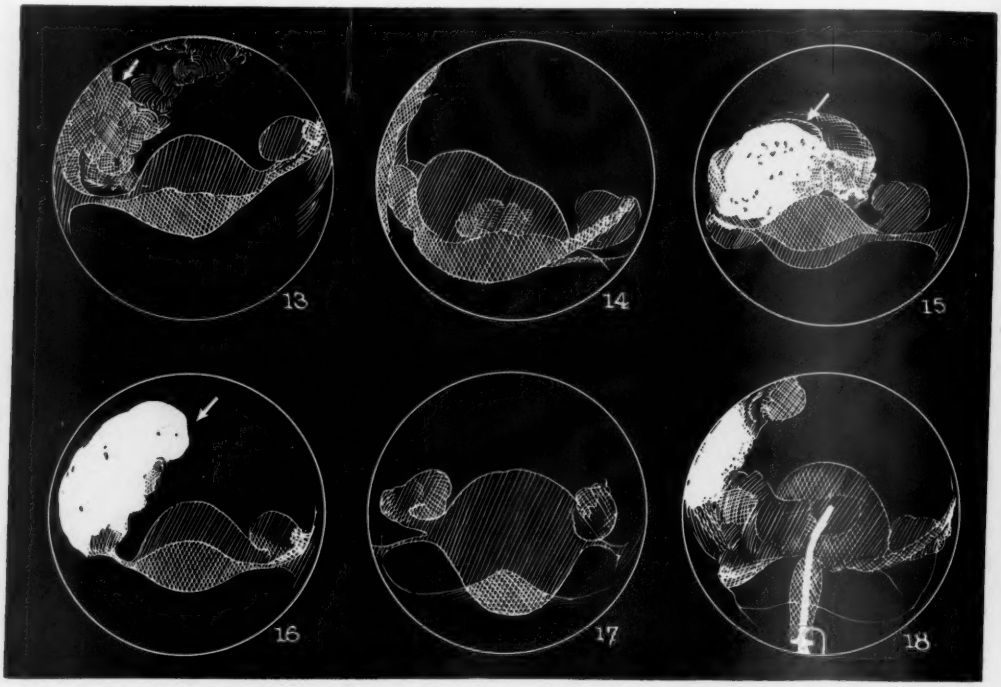

Fig. 3.—*13*, Right unruptured tubal pregnancy: slight bleeding fimbriated end: *14*, intrauterine pregnancy, 7 weeks: symptoms simulating ectopic produced by oxytocic drugs; *15*, right tubal pregnancy: partial tubal abortion; *16*, right tubal pregnancy: unruptured; *17*, intrauterine pregnancy, 6 weeks, acute anteflexion; *18*, right tubal obstruction: inflammatory disease (postabortal).

opposite adnexa appear normal, the tube and ovary being visualized. The uterus in some cases appears larger, and in some, normal in size. In cases where there has been pre-existing inflammatory disease, there will be increased density of both tubal shadows, and then the change in size and shape will be significant in diagnosis. When previous bilateral tubal damage has occurred and extensive pelvic adhesions are present, the picture is likely to be confusing. A small amount of blood in the peritoneal cavity does not interfere with the diagnosis in early unruptured and suspected tubal pregnancy. While the transuterine route is not used in suspected cases, in cases of old quiescent tubal pathology where the diagnosis of an ectopic must be considered, I have

combined the instillation of opaque media into the uterine cavity with the pneumoperitoneum to obtain complete gynecography of the pelvis (Fig. 5). In a few such cases, the combined method has proved of value in arriving at a correct diagnosis. Here we may observe that the contrast medium either stops abruptly at the point of tubal obstruction (by the implanted ovum) or *it breaks up into numerous small channels where it permeates the blood clot.* I have never observed that it surrounds the ovum in the tube in the characteristic way described by Mathieu. The greater information from this procedure accrues from the use of pneumoperitoneum, for the latter permits outlining the tubal

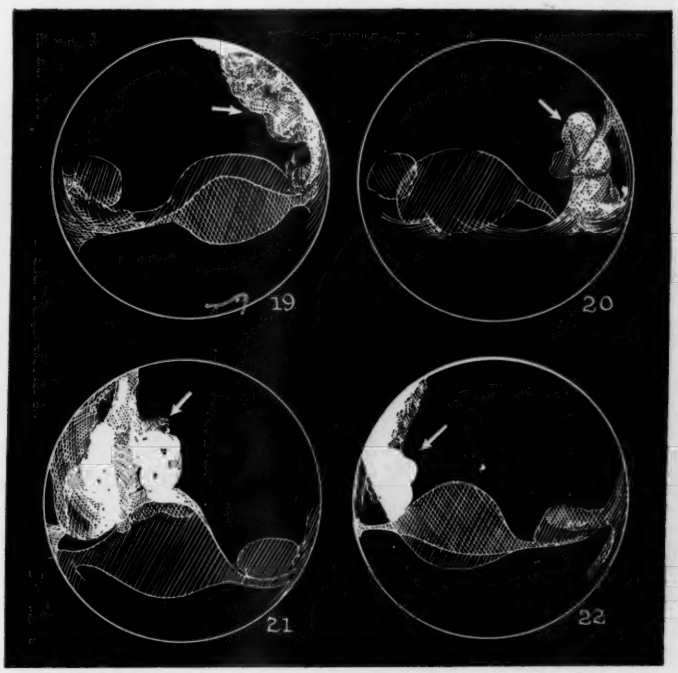

Fig. 4.—*19*, Left tubal pregnancy: unruptured; *20*, left tubal pregnancy: unruptured; *21*, right tubal pregnancy: partial tubal abortion; *22*, right tubal pregnancy: unruptured.

mass on the x-ray film. In one of our cases, hysterosalpingography was used first and was of no diagnostic value alone, but when pneumoperitoneum was performed in addition, the adnexal mass was recognized as characteristic of a tubal mole (Fig. 5).

In this communication, 15 cases of early ectopic pregnancy are presented and illustrated (Figs. 1 to 4) in which gynecography was of distinct aid in diagnosis. Another group of cases is shown by way of contrast in which the symptoms were suggestive of ectopic pregnancy and in which the evidence from the x-ray film was sufficient to rule out the diagnosis of ectopic pregnancy. It is just as true of x-ray as of other diagnostic methods, that one must evaluate the findings in the light of

symptoms and other signs as well as correlating the history of the case in order to arrive at a correct diagnosis. In no case was entire dependence placed upon this one diagnostic procedure. In some, however, the gynecographic evidence was the *deciding* factor in determining treatment. That some conclusions drawn from the x-ray films were erroneous must be admitted, but these were errors of interpretation. In other instances, the films were of no diagnostic value whatsoever. In addition to aiding the positive diagnosis of ectopic pregnancy in some cases,

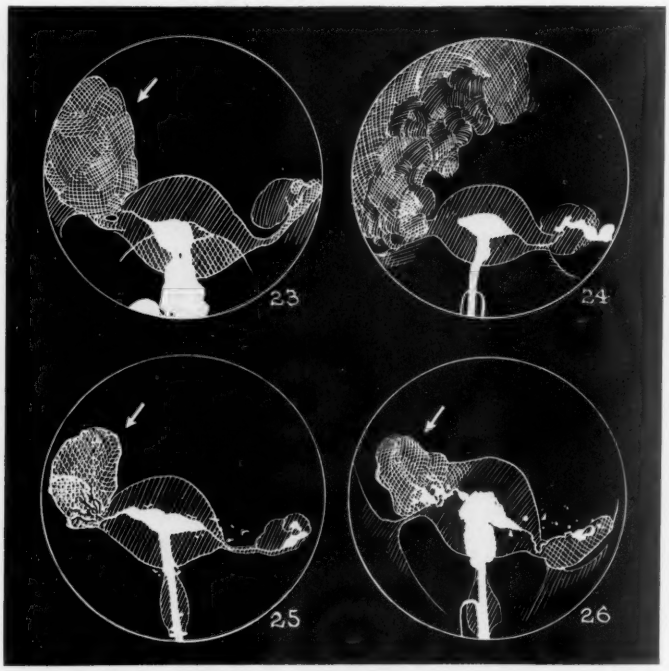

Fig. 5.—Combined gynecography. *23*, Old unruptured tubal pregnancy: tubal mole; *24*, unilateral inflammatory disease: simulating picture of tubal pregnancy on film; *25*, right tubal mole: note dispersion of contrast medium upon entering blood clot in tube; *26*, interstitial pregnancy right horn (mole): note dispersion of contrast medium in clot.

gynecography was instrumental in ruling out this diagnosis and at the same time, establishing that of another pelvic condition, i.e., intrauterine pregnancy, cystic ovary, etc. Hence, the method possesses both a positive and a negative value in the diagnosis of ectopic pregnancy.

CONCLUSIONS

1. Gynecography may be beneficially employed in the diagnosis of early and unruptured ectopic pregnancy.

2. Transabdominal pneumoperitoneum is more valuable, more informative, and less harmful than hysterosalpingography.

3. The two methods may be combined in selected cases with excellent results.

4. Unruptured tubal pregnancy can be shown on the pneumogram with sufficient clarity to serve as a positive means of diagnosis.

5. Gynecography has a negative value in the diagnosis of ectopic pregnancy in that it may show definitely intrauterine pregnancy with normal adnexa, ovarian cyst, and/or other lesions to account for the patient's symptoms, and thus rule out the presence of ectopic pregnancy.

I wish to acknowledge my gratitude to my colleagues on the gynecologic and roentgenologic services at Michael Reese Hospital for their permission to include their cases, and for their cooperation; and to Dr. Harold Laufman for the illustrations.

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310 South Michigan Avenue

THE USE OF UTERINE PACKS IMPREGNATED WITH SULFANILAMIDE*

A Preliminary Report

HARLEY E. ANDERSON, M.D., HERMAN L. GARDNER, M.D.,
M. F. GUNDERSON, PH.D., AND J. M. SLACK, PH.D., OMAHA, NEB.

(From the Departments of Obstetrics and Gynecology and Bacteriology, University of Nebraska College of Medicine, University Hospital)

UTERINE packing as a tamponade in the puerperal uterus for the prevention of severe hemorrhage is an old procedure.

Leroux is credited[1] with first inventing the uterine tamponade in 1776, but Dührssen popularized[2] its use in 1887. Plain sterile gauze, and gauze to which various chemicals have been added, with the hope that their bactericidal action might sterilize the uterine cavity, have been used extensively. The most popular sterilizing agents in the uterine pack are iodoform, iodine, lysol, and hexylresorcinol, favored by various writers. DeLee[1] advocates 0.5 per cent lysol packing; Dührssen was the first to suggest[2] the use of iodoform gauze and has since had many followers, while Torpin[3] feels that hexylresorcinol solution is an excellent bactericide in a uterine pack; Beck,[4] however, suggests the use of moist sterile packing with no chemical bactericide, and Stander[2] prefers plain, sterilized gauze to that impregnated with iodoform or other antiseptics.

Various means of introducing the pack within the uterine cavity have been suggested by numerous operators.

Holmes,[5] in 1902, introduced a mechanical uterine packer by means of which the uterus could be snugly packed. Torpin[3] has recently modified the Holmes packer so that a larger quantity of gauze may be stored in a mechanical reservoir, and also various forms of liquid antiseptics may be added at the time of packing. DeLee[1] used the uterine dressing forceps, while Beck[4] and Schumann[6] stress the manual method of packing.

The sole purpose of the uterine pack is to control hemorrhage when all other means have failed to check uterine bleeding. It is not the purpose of this paper to discuss the use of uterine packing in any but post-partum bleeding. It is in the atonic uterus that the tamponade acts most effectively and dramatically. Its action is twofold in that it exerts pressure upon the bleeding vessels, as well as mechanically stimulates the uterus to vigorous contractions. The majority of authorities concede that in the atonic uterus, after such measures as

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The sulfanilamide used in this study was generously supplied through the courtesy of Eli Lilly and Company.

massage of the organ, exhibition of pituitary extract, and intravenous use of ergonovine have failed to control post-partum or post-abortal hemorrhage, no time should be lost and the uterus should be packed promptly.

Schumann[6] admonishes haste in packing and advocates not waiting until signs and symptoms of acute anemia appear. Dorsett[7] believes that too late packing fails to control bleeding, because, after the patient has lost a large quantity of blood, the uterus will not contract properly on account of atonic musculature and marked anemia; he therefore urges packing the uterus at the first sign of abnormal bleeding. Torpin[3] states that the routine use of pituitrin and ergonovine is insufficient, since in his experience in a series of 200 cases in labor there was sufficient bleeding to be classed as post-partum hemorrhage; of this series 11 cases required uterine packing, notwithstanding the routine use of pituitrin and ergonovine. It is generally agreed that any amount of blood in excess of 500 c.c. lost at the time of delivery is considered post-partum hemorrhage.

A number of factors influence the likelihood of abnormal post-partum bleeding.

Davis[8] considers improper conduct of the third stage of labor the most common etiologic factor in hemorrhage. He also thinks prolonged anesthesia and analgesia produce a marked lack of uterine tone and motility, thereby increasing the hazards in the third stage of labor. Long labors are a marked factor, as well as unusual operative interventions like version and extraction, difficult forceps deliveries, etc. He cautions that packing the uterus includes a considerable hazard of infection in the invasion of the uterus, but that delay in packing involves an even greater hazard because of the continuing blood loss.

Trauma and hemorrhage within the uterine cavity are the two chief predisposing factors in puerperal sepsis. No matter with what gentleness the pack is introduced into the endometrial cavity, there is certain to be a large amount of definite injury to the compact layer of the decidua. To understand better the damage produced by the traumatic invasion of the uterus by a foreign object, it may be well to describe the appearance of the uterus at the completion of the third stage of labor.

According to Watson,[9] "The lining of the uterus is a continuous raw surface, more or less shaggy, incident to the separation of the decidua through the spongy layer. At the placental site, thrombi project to the large venous sinuses, giving this area a roughly elevated appearance. While some of the sinuses are occluded, some of them remain open, excessive bleeding from them being controlled by firm contraction of the uterine wall. In the course of the first week of the puerperium, a necrosis occurs in the superficial layers of the decidua, and this necrotic tissue is cast off with the lochial discharge, while active proliferation of the cells goes on in the deeper part, next to the uterine muscle, to form

the new mucosa.'' Thus, the whole lining of the uterus is simply a granulating surgical wound.

It is therefore easy to understand that any organisms present find an ideal nidus for their growth during the early stage of this ''casting off and granulating process.''

Watson[9] further states, ''Organisms are present in abundance in the superficial necrotic tissue, in the thrombi, and in any retained pieces of placenta or membrane. Underneath this layer is the remains of the decidua compacta, and in it an active reaction is taking place, being crowded with leukocytes. There is some edema, and thus a barrier zone is set up which prevents an extension of the organisms to the deeper levels.''

In other words, this area is nature's first line of defense against infection, and if this protective barrier is not broken through, or removed by a process which may denude it, infection will be halted here and will not be spread further through the lymphatics or blood stream. Often, after removal of the uterine pack, bits of tissue were found scattered over the surface of the pack material. Suspicion that this tissue was composed of fetal and/or maternal membranous elements led to microscopic examination.

We have been able to show pieces of decidua and placenta embedded within the meshes of the gauze when the uterine pack was removed (Fig. 1). This protective zone had thus been loosened and carried away on the pack by a curettage-like action. The most dangerous form of treatment as far as infection is concerned is to curette the puerperal uterus. The pack usually is removed in from forty-eight to seventy-two hours after its introduction, and at this particular time, as shown by Armstrong and Burt-White[10] and others, the uterus is teeming with organisms. Inasmuch as nature's barrier against infection is undoubtedly removed at least partially at the time the pack is withdrawn, it would seem reasonable to wish for some agent that might curb the pathogenic action of the existing organisms by its bacteriostatic action.

It has been long recognized that the introduction of any foreign object into the uterine cavity, immediately after the third stage of labor, increases the incidence of puerperal infection. For this reason various types of antiseptics have been employed in uterine packs with the hope that the action of the chemical, through its bactericidal action, would diminish the incidence of sepsis. In the experience of the senior author (H. E. A.), both plain sterile gauze and iodoform have been used to control bleeding and on occasion severe puerperal infection has followed removal of the pack. For that reason it was thought advisable, because of the bacteriostatic action of sulfanilamide, to attempt to impregnate gauze with this drug and to study experimentally its clinical action upon patients as well as its action upon the organisms within the uterine cavity.

The idea of using sulfanilamide for its bacteriostatic action in surgical wounds was first suggested by Jensen, Johnsrud and Nelson[11] in their report of a series of 39 compound fractures and 2 compound dislocations treated by local implantation of sulfanilamide. After completion of meticulous debridement, crystalline sulfanilamide (5 to 15 Gm.) was introduced into the wound, which was then closed with interrupted silk sutures. In this series there was no instance of primary wound infection, a much better record than would ordinarily be expected in a series of contaminated fractures. Since then, numerous articles have been published concerning the beneficial action of sulfanilamide in many types of surgical wounds.

SULFANILAMIDE IMPREGNATED GAUZE PACKS

The length of the pack used in this experimental study was four and one-half feet. We are fully aware that this is an insufficient length completely to pack an atonic uterus for hemorrhage; however, in this series there were only four instances of atonic uterus; therefore, four

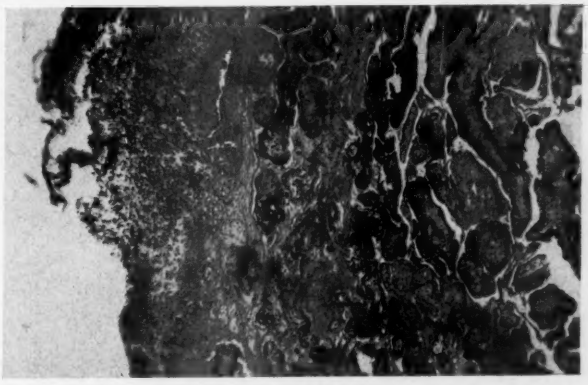

Fig. 1.—Material obtained from within meshes of uterine pack, showing marked polynuclear infiltration, decidual cells, and large amount of chorionic villi.

and one-half feet were of sufficient length to pack completely the tonic uterus. The original thirty-six inch wide plain gauze is folded into 16 complete folds so that the width of the strip as it is inserted into the uterus is 2½ inches, the selvage edge being on the inside. Inasmuch as sulfanilamide is so little soluble in water, we found it best to soak the roll of gauze in water and wring out the excess moisture to the point that no water would drip. The pack was then opened and placed upon a flat surface, as shown in Fig. 2, and the contents of two-five gram sterile ampoules of sulfanilamide were distributed equally and thoroughly throughout the surface of the moist pack; the sulfanilamide was then rubbed into the meshes of the gauze so there was an even distribution throughout the length as well as the width of the pack. A small cotton ball measuring about 2 inches by 1½ inches, to which a small piece of black linen thread had been tied for identification (Fig. 3), was then placed within the inner folds of the gauze, about nine inches from the end of the pack that would be placed nearest the fundus of the uterus, in such a position that only two layers of gauze separated the ball from the uterine cavity. The purpose of the cotton ball is to obtain

intrauterine cultures, and will be described more fully later. For identification, a numbered metal tag was attached by a string to the other end of the gauze pack. The pack was then rolled upon itself, starting with the tag end first, so that it would be ready to be inserted into the uterus when unrolled. It was then sterilized by the autoclave at 255° F. for thirty minutes under 20 pounds of pressure.

A pack similar to the one described above, with the exception that sulfanilamide was not added, was used as a control. Iodoform gauze packing was also used and made up in a similar manner, with 10 per cent iodoform and a cotton ball encased within its meshes. The total number

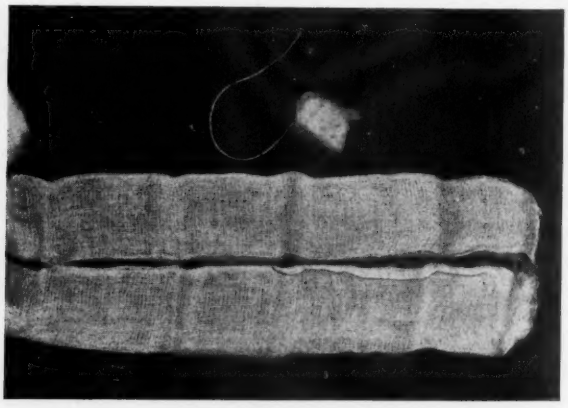

Fig. 2.—Moistened pack ready for impregnation with sulfanilamide powder. Cotton ball not inserted until after sulfanilamide is thoroughly distributed through pack.

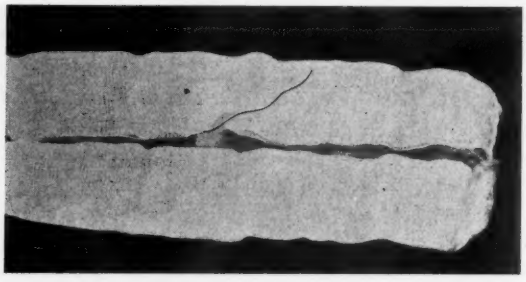

Fig. 3.—Position of cotton ball as inserted within folds of gauze, also its location with regard to the end which is inserted into the fundus.

of packs used in this study was 80. However, the first 10 were not checked by intrauterine cultures and for that reason tabulation of clinical results is computed on only 70. Of these, 37 were sulfanilamide packs, 27 plain packs, and 6 iodoform packs.

METHOD OF INTRODUCTION INTO THE UTERUS

The patient's legs were supported by stirrups. In each case in this series the following technique of introduction of the intrauterine pack was adhered to:

After the third stage of labor an anterior and posterior vaginal speculum was introduced and held as a retractor by an assistant. A ring

forceps was used to grasp both the anterior and posterior lips of the cervix, and by gentle traction the cervix was pulled down into the neighborhood of the vaginal introitus. The anterior speculum was then removed, but the posterior speculum was left in place to protect the pack from touching the anus. The pack was grasped by another ring forceps

Fig. 4.—Pack rolled, showing numbered metal tag. Actually the tag end is rolled up first in order that the opposite end containing the cotton ball may be inserted in the region of the uterine fundus.

Fig. 5.—Showing the folds of the pack open in preparation to removing the cotton ball with the hemostat.

and packed snugly into the uterine cavity, after the free hand of the operator had firmly grasped the uterus through the abdominal wall, in order to steady the uterus from above and thereby discourage any tendency toward perforation. The entire pack was inserted into the uterine cavity and the string with the metal tag was left hanging

through the cervix and into the vaginal canal. Of course, knowledge of the direction of the cervical and uterine passage facilitates greatly the ease with which the uterus is packed. We found more difficulty in inserting a pack into the tonic uterus than into the relaxed bleeding uterus; the difficulty, of course, was produced by the pressure of the tone of the uterine wall. Usually, when the pack is within the uterine cavity, the patient complains of malaise, with or without low grade fever at times. It was not uncommon to have chills accompanying this fever within a few hours after the pack was inserted, and early in our series we removed two or three packs, but we subsequently found that the fever was not necessarily a dangerous sign. Less fever was also noted when the pack remained completely within the uterine corpus than if it had slipped down and had obstructed the cervix. In no case in this series was a pack used if the patient was frankly or potentially infected before insertion of the pack.

REMOVAL OF THE PACK

The average length of time that packs were allowed to remain in the uterus was as follows: Sulfanilamide 54½ hours; plain 43 hours, and iodoform 42½ hours. To remove the pack, the examiner's hand was encased in a sterile rubber glove, the first two fingers were introduced into the vagina, and the metal tag was firmly grasped. It was noted at this time whether any of the pack had been expelled into the vagina or not. Gentle traction was then made upon the pack and a minute or two consumed in removing its entire length. If, for any reason, there was difficulty in withdrawing the pack, the operation was stopped for a minute or so, then again resumed so that as much as five minutes was consumed at times in the removal of the pack. When the piece of black thread came into view, the edge of the pack was grasped by a sterile hemostat and the folds of the pack were opened (Fig. 4). From the cotton ball, grasped by another sterile hemostat, a small portion was excised by a pair of sterile scissors. This small excised portion of the cotton ball was then streaked over a blood agar plate and sent to the laboratory.

MORBIDITY

With morbidity represented by a temperature of 100.4° F. or over, it was interesting to note the following uncorrected morbidity. In the plain pack there was 72 per cent, in the sulfanilamide 38 per cent, and in the iodoform 20 per cent. In the sulfanilamide group, one patient had a severe paronychia during the first five post-partum days, and ran a temperature of 102° F. Another patient had acute sinusitis, with a temperature of 104° F. following delivery: the third was thought to have an acute appendicitis, but instead, in the region of the infundibulopelvic ligament, a hematoma was found, which in the operator's judgment, was not produced by the uterine pack. All rises of temperature of patients in the plain pack group, in our estimation, were directly due to the use of the packs. Two of these cases had a rather severe acute endometritis and the bacteriology in both showed nonhemolytic streptococci aerobically and *Staphylococci aureus* and *albus* on anaerobic culture. Both were treated with sulfathiazole and recovered.

One patient in the iodoform group on the second post-partum day showed a temperature of 100.4° F., which promptly subsided. The only organisms found both aerobically and anaerobically were nonvirulent diphtheroids.

RUPTURE OF MEMBRANES

The incidence of intrauterine infection is directly proportional to the time elapsing between the rupture of the membranes and the time of delivery; therefore, the ratio of infection upon this basis was greatly increased in the sulfanilamide group, because the length of time was ten hours and forty minutes; in the group of plain packs four hours and forty-two minutes; and in the iodoform group the time was twenty-four minutes.

TABLE I. TYPES OF DELIVERY

SULFANILAMIDE	PLAIN	IODOFORM
(a) 31.9% spontaneous	(a) 37% spontaneous	(a) 60% spontaneous
(b) 9.4% spontaneous with episiotomy	(b) 7.25% spontaneous with episiotomy	(b) 20% spontaneous with episiotomy
(c) 35.2% low forceps with episiotomy	(c) 33.5% low forceps with episiotomy	(c)
(d) 11.8% low forceps	(d) 18.75% low forceps	(d) 16% low forceps
(e) 5.8% frank breech with forceps to head	(e)	(e) 4% frank breech with forceps to head
(f) 5.8% forceps rotation posterior position	(f)	
	(g) 3.5% internal version and breech extraction	

BLOOD SULFANILAMIDE LEVELS

The purpose of this study was solely to note the bacteriostatic action of sulfanilamide within the uterine cavity, with no hope of obtaining a generalized action from the drug. However, we were curious to ascertain whether or not some of the drug was absorbed through the uterine mucosa, as we might expect, because of the nearness and abundance of the blood supply within the uterus. Blood sulfanilamide levels were therefore run on selected cases early in the series. This was soon discontinued because of the unanimity of results obtained on the blood levels.

TABLE II

Case 1, left in 53 hr.		
24 hr., 0.3 milligrams %		
48 hr., none		
Case 2, left in 52½ hr.		
4 hr., 8.8 milligrams % free		1.0 milligrams % total
45 hr., 0.5 milligrams % free		1.3 milligrams % total
Case 3, left in 49½ hr.		
23 hr., 3.1 milligrams % free		4.6 milligrams % total
48 hr., 0.9 milligrams % free		2.5 milligrams % total
Case 4, left in 52 hr.		
25 hr., 1.2 milligrams % free		2.3 milligrams % total
48 hr., 0.5 milligrams % free		1.3 milligrams % total
Case 5, left in 48 hr.		
6 hr., 1.3 milligrams % free		1.9 milligrams % total
29 hr., 1.9 milligrams % free		2.3 milligrams % total
48 hr., 1.4 milligrams % free		0 milligrams % total
Case 6, left in 44 hr.		
3 hr., 1.7 milligrams % free		1.8 milligrams % total
26 hr., 2.2 milligrams % free		4.7 milligrams % total
46 hr., 2.0 milligrams % free		0 milligrams % total

Case 7, left in 60 hr.	
34 hr., 1.5 milligrams % free	2.5 milligrams % total
Case 8, left in 48 hr.	
21 hr., 3.5 milligrams % free	6.1 milligrams % total
42 hr., 3.6 milligrams % free	5.0 milligrams % total
Case 9, left in 54 hr.	
3½ hr., 1.3 milligrams % free	1.8 milligrams % total
Case 10, left in 57 hr.	
30 hr., 2.0 milligrams % free	
58 hr., 0.3 milligrams % free	0.6 milligrams % total

ODOR

If the sulfanilamide pack had no therapeutic virtue other than removing vaginal odor, the use of sulfanilamide in a pack would be justified. Almost without exception in the sulfanilamide packs, there was no odor about the patient while the pack was in the uterus or at the time of withdrawal. However, the converse was true with the plain pack; in most instances the odor was very foul and was complained of by both the patient and nursing staff. The iodoform pack reeked of the characteristic odor of the drug, but at no time could a foul odor due to lochia be detected.

BACTERIOLOGY

Two types of media were employed for the cultivation of the organisms found in the cotton balls. The first, blood agar, was 10 per cent goat's blood in veal infusion agar. The second was Brewer's[12] medium. This is a pork infusion broth containing 0.05 per cent agar, 0.1 per cent sodium thioglycollate, and the indicator, methylene blue. The sodium thioglycollate is the active ingredient so far as maintaining anaerobic conditions are concerned.

Approximately the upper 1 to 2 cm. is aerobic, and here the methylene blue has a green color. Thus, it is possible to cultivate aerobic, microaerophilic or anaerobic organisms in this one liquid medium.

The cotton balls, which have been previously described, are particularly adaptable to such an investigation. They are small, of uniform size, and can be easily inserted or withdrawn. Being placed in the folds of the pack they provide as nearly as possible a true picture of the bacteriologic flora of the pack. Immediately following their removal they were streaked over the entire surface of a blood agar plate. They were then immersed in Brewer's medium and squeezed against the side of the tube so that the medium was sure to be inoculated. The cultures were then incubated at 37° C. for twenty-four hours. If no growth was present at this time they were observed at various intervals for one week and then discarded.

Table III shows the organisms found and the frequency with which they occurred in the three different packs.

TABLE III

ORGANISMS FOUND	PLAIN (27)		SULFANILAMIDE (37)		IODOFORM (6)	
	PLATE	BREWERS	PLATE	BREWERS	PLATE	BREWERS
No growth	2	–	15	2	–	–
Streptococcus (Nonhem.)	6	7	8	7	1	1
Streptococcus (Hem.)	4	4	1	–	1	2
S. albus	13	13	6	10	3	2
S. aureus	6	2	–	–	–	–
Diphtheroid (Nonvir.)	7	4	7	8	1	1
E. coli (Hem.)	2	2	–	–	1	2
E. coli (Nonhem.)	2	2	–	–	1	1
Anaerobic Staph.	–	2	–	3	–	–
Anaerobic Strep.	–	–	–	4	–	–
Spore former	5	2	–	–	–	–
St. viridans	–	–	1	1	–	–
A. aerogenes	–	–	–	–	1	1
Sarcina lutea	1	1	–	–	–	–
Unident. gram-negative rod	1	1	–	1	–	–

This table shows, in the sulfanilamide packs, bacteriologic flora markedly different from the flora of other packs. The sulfanilamide packs gave more blood agar plates with no growth and significantly showed a marked diminution in the growth of the hemolytic streptococcus aerobically, while no growth at all was obtained in the anaerobic culture. In addition, the *E. coli* (both hemolytic and nonhemolytic) and the spore formers were absent both aerobically and anaerobically. All these factors are in sharp contrast to bacteriologic findings for the plain and iodoform groups.

SUMMARY

1. Various types of uterine packing have been reviewed, either plain or impregnated with some chemical. Likewise, various means of introducing the pack within the uterus have been described.

2. The sole purpose of the uterine pack is to control bleeding in the atonic uterus after other means have been used as oxytocics.

3. Delay in the use of the uterine tamponade very often results in a fatality.

4. The introduction of any foreign object into the uterus increases the incidence of infection. The withdrawal of the uterine pack produces a curettage-like action at the time when the uterine cavity is teeming with bacteria.

5. The purpose of the use of sulfanilamide impregnated gauze packs is prophylactic against infection because of the bacteriostatic action of the drug at the site of contact with tissue.

6. The technique of impregnating the gauze pack with sulfanilamide is described and discussed.

7. The use of a small cotton ball, encased within the meshes of the uterine pack, serves as a very satisfactory means of obtaining both aerobic and anaerobic intrauterine cultures.

8. In our judgment, grasping the anterior and posterior lips of the cervix with ring forceps, thereby bringing the cervix directly into view, and snugly introducing the gauze into the uterine cavity by means of a third ring forceps is the most acceptable manner of packing the uterus.

9. There is a general diminution in the number and kinds of bacteria in general, and of the hemolytic streptococci and *Staphylococcus aureus* in particular, when sulfanilamide is used to impregnate the intrauterine pack. Clinically, the plain pack, used as an intrauterine tamponade, increases morbidity above that of either the sulfanilamide or iodoform pack.

10. This preliminary series is small, from a bacteriologic standpoint, and a larger number of cases is desirable before definite conclusions are drawn. However, from the fact that sulfanilamide gives a much more sanitary pack, tends to decrease the bacterial flora, inhibits growth of hemolytic streptococci, and is absorbed to a limited degree into the blood stream, it seems advisable to use sulfanilamide packs in preference to either plain or iodoform, when indicated.

The blood sulfanilamide levels in this series were done under the direction of Dr. V. M. Wilder.

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DISCUSSION

DR. RUDOLPH W. HOLMES, University, Va.—Dührssen formulated the indications and the method for the introduction of uterovaginal tampons for post-partum hemorrhages in the mid eighties, but general acceptance of his advice by the American obstetricians was only realized early in this century. I, myself, employed tamponades from the very beginning of my practice. At first, we all used sterile gauze and quickly learned its value as a means of controlling hemorrhage, but appreciated also that the gauze must not only be sterile but must be, to a degree, definitely antiseptic. If the gauze were not impregnated with a germicide it became very foul before it was extracted, showing that saprophytes developed in the gauze, and there was evidently the possibility of a virulent infection developing from its use. Gauze saturated with a 1:10,000 bichloride solution or "washed" iodoform gauze produced similar results. Both of these chemicals were also decidedly objectionable in that they were readily absorbable poisons. After trying all kinds

of antiseptics, we found that a certain proprietary preparation was the most efficacious, but its expense for each tampon was prohibitive. A gauze wet with weak liquor cresolis compositus was distinctly valuable, as the drug was inexpensive and always available.

I would stress that saturation of a sterile gauze with an antiseptic solution is not a sufficient precaution. Other requirements are the following: the impregnated gauze must be sterilized in a permanent container (i.e., a quart wide mouth jar with a glass top); the antiseptic must not be decomposed by the high temperature of an autocalve; the drug shall not be of a potency or type poisonous to the woman; the gauze should be 12 feet long and 18 inches wide, the raw edge folded within the pleats and the strip finally not much more than two inches wide.

There are a number of variants in the technique of introducing the gauze, but even with the vagina widely opened by large specula and ring forceps applied to the anterior and posterior lips of the cervix, there is always an inherent danger that the gauze will scrape on the skin or mucosa. There is a further danger that the gauze as it passes over the cervical canal will so irritate the uterus to contract that the tamponade may be introduced only with difficulty, or even be prevented by the tightly retracted lower segmental ring. To obviate these difficulties and dangers I devised in 1899 a special tube sufficiently large to carry the ribbons of gauze 2 inches wide. For insertion of the instrument the tube had an obturator which could be removed after which, with an *introducer* the gauze was placed in situ. The great advantage of this tube was that the gauze only touched boiled surfaces from the moment of its exit from the glass container until it was in contact with the uterine mucosa.

If there be atony, the uterus should not be overpacked, for if the pack be too tight it will prevent retraction of the uterus. It must be appreciated that the pack serves a double purpose, namely to dam the bleeding vessels and to stimulate the uterus to contract and retract. The gauze should invariably be in one piece, and never be left more than twenty-four hours. If fearful of a recurrence of hemorrhage, be prepared to tampon again at the time the gauze is removed.

DR. H. CLOSE HESSELTINE, CHICAGO, ILL.—It takes, of course, quite a number of cases to work out the statistical advantages of a new procedure. Dr. Anderson found it necessary to use many normal patients to make this study, for in the usual course of events it would take a long time to have a sufficient number that had to be packed.

The need for packing in a properly managed case is very infrequent. Prior to the introduction of ergonovine, less than 1 per cent of the parturient patients on our service were treated by intrauterine pack. M. Edward Davis has a report in progress which indicates that the need for pack has now been reduced 90 per cent. This agrees in part with Dr. Diddle's paper earlier this morning.

In regard to the chemical substances used, the method of sterilizing the pack must be carefully considered, for overheating may cause the drug to change. Toxicity to the mother must be thought of, for one of our patients developed nephritis following the insertion of a pack moistened with one-half per cent lysol solution.

I would like to ask Dr. Anderson whether the patients had any irregularities in menstruation after the menstrual cycle was established. Probably there will be no special damage within the intrauterine cavity but one should investigate for such residual injury.

The question should be raised as to which one of the sulfonamides is most valuable (sulfanilamide, sulfapyridine, sulfathiazole, sulfadiazine, and sulfaguanidine). Sulfaguanidine is the most insoluble and has been used quite successfully in intestinal

surgery, and perhaps sulfaguanidine might be better in the uterus. Sulfadiazine appears more toxic than sulfathiazole and sulfathiazole is better tolerated than sulfapyridine.

One should not rely upon the sulfonamides to correct one's techniques. The prolonged period during which the pack was left in the uterus by the writers may be criticized. We seldom leave a pack for more than eighteen hours.

DR. ANDERSON (closing).—The sulfanilamide pack on removal has absolutely no odor. For that reason alone the sulfanilamide pack would merit use instead of either the plain or iodoform pack.

We made some quantitative chemical tests to see whether the sulfanilamide was lost in the sterilization. We analyzed an impregnated pack chemically and found that, out of the 10 Gm. which were put in, there were returned some 8.5 to 9 Gm. of the drug.

With regard to possible later disturbances of menstruation, I have no information.

PREMATURE RUPTURE OF MEMBRANES*

A Clinical Study

J. H. Morton, M.D., C. S. Peabody, M.D., John Newdorp, M.D., and Fred L. Adair, M.D., Chicago, Ill.

(From the Department of Obstetrics and Gynecology, the University of Chicago and the Chicago Lying-in Hospital)

WHENEVER a pregnant patient is observed who is not in labor and in whom the amniotic sac has ruptured and the fluid has been lost, a problem concerning the most satisfactory management immediately presents itself. Because of a clinical interest in these patients with premature loss of fluid and in the associated conditions which may result from early rupture of membranes, we have reviewed a series of such cases in order to study the possible changes in uterine physiology, the effects of dry labor, and the results obtained by various methods of management.

MATERIAL

One thousand histories of women delivered at the Chicago Lying-in Hospital in whom the membranes ruptured prior to the onset of labor were obtained. They were consecutive and unselected except for this one requirement. Chemical tests were not usually used to determine or confirm the diagnosis of premature rupture and the clinical diagnosis plus the confirmation of previous rupture at the time of delivery were used as the criteria. Because of the elimination of questionable cases as far as possible, an incidence figure for premature rupture is not attempted.

The scatter chart (Fig. 1) indicates the case distribution of the 1,000 patients in regard to the period of gestation in weeks and the latent

*Presented at the Thirteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, New Orleans, La., October 2 to 4, 1941.

period in hours before the onset of labor, as well as fetal mortality which was associated. The latter are circled in black, those with 2 black circles indicating dead infants having evidence of lung infection at autopsy.

Of these patients, 536 were primiparas and 464 were multiparas; 71 had artificial rupture of membranes, and in the remainder rupture occurred spontaneously. One hundred and eighty-two patients had castor oil, quinine, pituitrin, bag, or a combination of these inductions superimposed on the already ruptured membranes. Although these compound inductions confuse the physiologic picture, they were included because of their possible clinical importance. Subsequent tables will show the analyses of these cases.

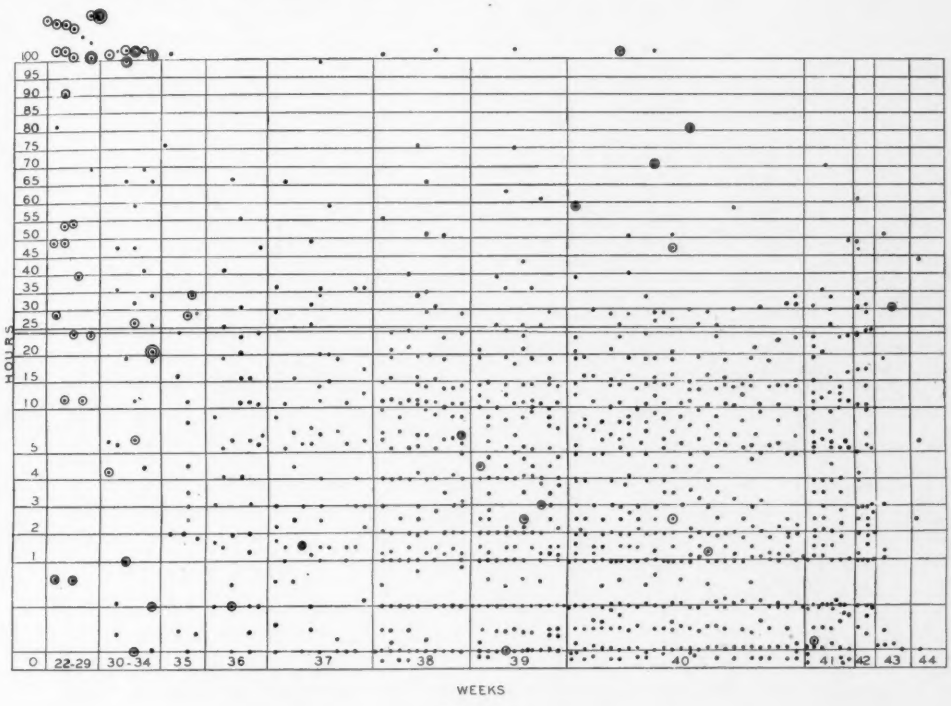

Fig. 1.

No particular effort has been made in this series to study the etiologic factors for the premature rupture. Factors which may possibly be significant, such as the presentation of the fetus and abnormal states in the mother, are shown in Tables I and II. Where available, the incidence of their occurrence in large hospital statistics is shown for comparison.

In this series 91.5 per cent of the cases had the vertex presenting in comparison with 94.95 per cent occurrence in the Chicago Lying-in Hospital series. There were proportionately more occiput posteriors (9.64 to 6.58 per cent) and breeches (6.5 to 4.2 per cent) while the incidence

TABLE I. POSSIBLE RELEVANT COMPLICATIONS

	NUMBER	PER CENT	INCIDENCE OF OCCURRENCE IN HOSPITALS C.L.I.H.
Toxemia	122	12.2	10.17
Contracted pelvis	35	3.5	3.65 (Mengert)
Placenta previa	4	0.4	0.9
Low lying placenta	6	0.6	
Abruptio placentae	7	0.7	7.7
Previous cesarean section	5	16.6	11.8 of 1000 c.s.
Heart disease	14	1.4	1.0+
Diabetes	6	0.6	0.10
Prolapsed cord	5	0.5	0.8 (Schiller)
Artificial rupture	71	7.1	—
Bag induction	20	2.0	—
Medical induction	162	16.2	—
Pyelitis	3	0.3	1.1
Polyhydramnios	3	0.3	0.34
Fibroids	2	0.2	12.0
Latent syphilis	7	0.7	2.5 (Williams)
Arrested tuberculosis	5	0.5	0.37
Hyperthyroid	1	0.1	0.07
Post-partum hemorrhage	16	1.6	2.5
Intra-partum infection	1	0.1	—

TABLE II. PRESENTATION—POSITION—MULTIPLE PREGNANCIES

	NO.	PER CENT		HOSPITAL
O.L.T.	279	27.46		94.95 (DeLee 35,179)
O.D.T.	214	21.06		
O.L.A.	147	14.46		
O.D.P.	98	9.64	Vertex 91.5	6.58
O.L.P.	83	8.17		5.92
O.D.A.	78	7.67		
Breech	66	6.50		4.20
[Twins]	12	1.18		1.18 (1934-1940 / 15,957 cases)
Compound	3	0.29		
Transverse	2	0.19		0.45
Face and Brow	2	0.19		0.45
Vertex (not indicated)	16			

of twins was the same (1.18 per cent), and that of transverses and deflexed attitudes was slightly less (0.19 to 0.45 per cent each). The incidence of contracted pelves, toxemias, placenta previa, premature detachment of the placenta, heart disease, and diabetes (see Table II) cannot be interpreted as being significant. Cesarean sections, prolapsed cords, and inductions of labor will be discussed elsewhere. Post-partum hemorrhages (500 c.c. and more) occurred in 1.6 per cent of the patients, which is slightly less than the hospital average.

Polyhydramnion was diagnosed only three times in this series and in two of these cases normal infants were delivered. In view of the relatively high incidence of malformations and erythroblastosis in this series, it seems possible that undiagnosed polyhydramnion has occurred and has been a factor in the early loss of the amniotic fluid.

Prolapse of the umbilical cord occurred five times and a partial prolapse once. The partial prolapse occurred at term and was associated with a breech presentation. A vaginal Voorhees bag was inserted and a living infant was delivered. One prolapse took place following spontaneous rupture of the membranes at thirty-seven weeks. The infant was in an O.L.A. position and was delivered alive but died two days later of pneumonia. The cord of a second twin prolapsed after delivery of the first twin at thirty-six weeks' gestation. A living infant was delivered by version and extraction. Two prolapses with fatal results occurred at thirty-three weeks; one of these took place when the membranes were artificially ruptured for treatment of a partial placenta previa, and the other occurred when the cord and an arm both prolapsed

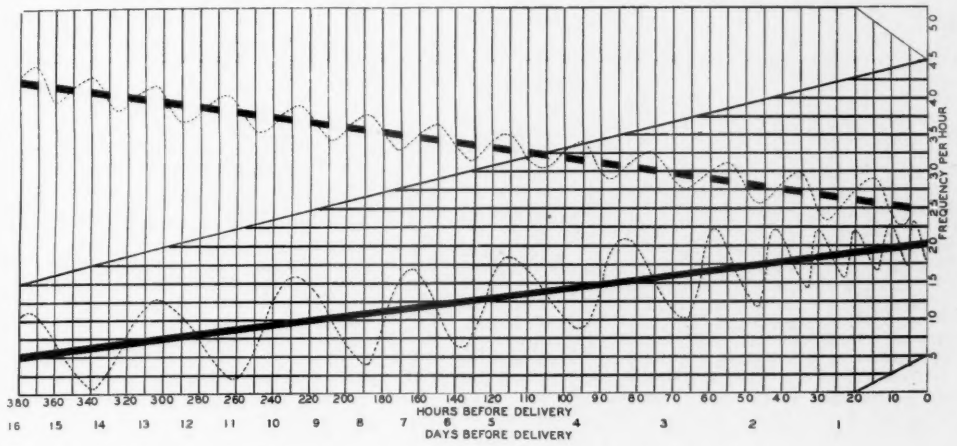

Fig. 2.

following spontaneous rupture, the infant being in a transverse presentation. In the sixth case spontaneous rupture occurred at twenty-eight weeks. The infant died, and a craniotomy was done to complete the delivery.

Thus all cases of complete prolapse occurred in relation to rupture of membranes prior to the expected termination of pregnancy, and none were found at term. For the series, the incidence of complete prolapse is 0.5 per cent.

UTERINE IRRITABILITY

It is well known that at different periods of gestation the uterus will respond differently to a given stimulus, and that there is a relative lack of irritability before term, causing increased difficulty in the induction of labor prior to the expected termination of pregnancy.

At the Chicago Lying-in Hospital, Dr. Con Fenning of the University of Utah made a careful study of over 500 patients, using external hysterographic methods, in an effort to determine the normal action of

human uterine musculature in vivo. Although this work is as yet unpublished, he has kindly given permission to use some of his illustrations and figures.

Fig. 2 shows the uterine activity in terms of frequency of contractions per hour for both small and large contractions. Note that as the time of delivery approaches, there is an increasing frequency of large contractions and a decreasing frequency of small contractions. He found, too, that after the membranes ruptured prematurely, there was an increase in the length and height of the contraction phase. This corresponds to the clinical observation that after the membranes rupture, labor pains become stronger; therefore, by rupturing the membranes at any given point, a shortening of the period that elapses before delivery occurs would be expected. The superimposition of oxytocic agents or

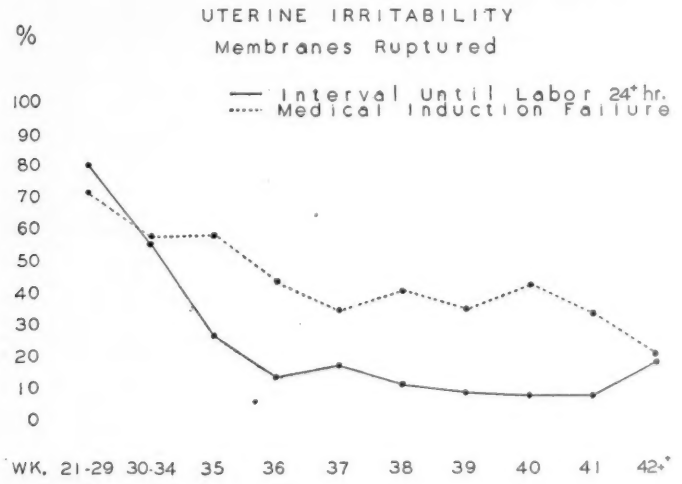

Fig. 3.

bags may further modify the action of the uterus, but the extent of alteration does not seem to have been satisfactorily demonstrated. The use of external hysterography definitely demonstrates that pituitrin can cause the uterus to contract at any phase of pregnancy which is sufficiently advanced to make possible the use of such an instrument; this does not mean, however, that labor will necessarily ensue.

The data regarding the latent periods between the time of rupture and the onset of painful contractions are shown for the 1,000 cases included in the present study in Table III. At term only 4.7 per cent of the primiparas and 7.3 per cent of the multiparas had latent periods of thirty hours or more. The actual length of these intervals is more apparent in Fig. 1. For instance, at 22 to 29 weeks, almost half (42.3 per cent) of the patients had latent periods of over one hundred hours with individual cases in this group running up to sixty-seven days. In the

TABLE III. LATENT PERIOD

WEEKS	PARITY	NUMBER		0-5 HR.		5-10 HR.		10-15 HR.		15-20 HR.		20-25 HR.		25-30 HR.		30+ HR.	
				NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
22-29	Primip.	10		1	10.0	0	0	0	0	0	0	2	20.0	0	0	7	70.0
	Multip.		12	0	0	0	0	1	8.3	0	0	1	8.3	1	8.3	9	75.0
30-34	Primip.	20		8	40.0	0	0	1	5.0	1	5.0	1	5.0	1	5.0	8	40.0
	Multip.		13	7	53.8	5	38.5	1	7.7	0	0	0	0	0	0	0	0
35-37	Primip.	62		33	53.2	6	9.7	4	6.4	4	6.4	3	4.8	1	1.6	8	13.0
	Multip.		57	24	42.1	10	17.5	5	8.8	3	5.3	4	7.0	1	1.8	10	17.5
38-44	Primip.	444		276	62.2	50	11.3	49	11.0	27	6.1	10	2.3	11	2.5	21	4.7
	Multip.		382	234	72.3	51	13.3	26	6.8	15	3.9	16	4.2	12	3.1	28	7.3
	Total	464	536														

MEANS IN HOURS

			SERIES	FENNING RUPT. MEMB.	FENNING "NORMAL"
38-44	Primip. 0-85 hr.	442	7.76 {7.04 s }	7.4	12.0
	Multip. 0-85 hr.	380	9.38 {8.07 induction}	20.8	7.9

group at term nearly 80 per cent of the patients were in labor within ten hours, 62.2 per cent of the primiparas and 72.3 per cent of the multiparas being in painful labor within five hours or less. It can be demonstrated with the hysterograph or by careful palpation that most of the patients going into labor soon after rupture of membranes are already having regular uterine contractions at the time membranes rupture even though they do not as yet feel pain. To give oxytocic agents to such patients could be dangerous. Patients in the entire groups that had more than a fifteen-hour latent period were unusual, and in these we would perhaps be justified in stimulating labor. We could at the same time better evaluate the usefulness of the induction.

The latent periods, both with and without the induced cases, compared with as yet unpublished figures of Dr. Fenning are shown at the bottom of Table III. The mean interval rises when the cases with medical induction of labor are added because more with prolonged latent periods are thus included. However, one would expect more dramatic results if the inductions had been highly successful in shortening the latent periods.

The irritability of the uterus in this series of cases, is shown more graphically in Fig. 3, the solid line representing the percentages of patients at different periods of gestation having latent periods of over twenty-four hours. The dotted line represents the percentages of failed medical inductions. This chart indicates the chances that any given patient with ruptured membranes will have of going for twenty-four hours without labor pains, and the chance there will be of not getting a satisfactory result following attempted induction with castor oil and quinine or pituitrin.

DURATION OF FIRST STAGE

The data pertaining to the length of the first stage of labor are shown in Table IV. Those patients that had operative intervention before complete dilatation of the cervix have been partially eliminated because of the inability to tell how long dilatation would have taken and when delivery would otherwise have occurred. The excluded cases include principally those with delivery by cesarean section and those in whom actual labor was never established. Those that had Dührssen's incisions were not excluded and appear largely in the group over thirty hours, thus not significantly altering the results. Because of the fact that the second and third stages are less pertinent to the discussion and because of possible modification of the figures as a result of the high percentage of operative deliveries and the use of ergonovine with delivery of the shoulders, no attempt has been made to evaluate or discuss this part of labor, except as noted under "Treatment."

At term we found that 76.3 per cent of the primiparas were fully dilated in less than fifteen hours and that 6 per cent required more than

TABLE IV. DURATION OF FIRST STAGE

WEEKS	PARITY	NUMBER		0-5 HR.		5-10 HR.		10-15 HR.		15-20 HR.		20-25 HR.		25-30 HR.		30+ HR.	
				NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
22-29	Primip.	8		2	25.0	4	50.0	1	12.5	0	0	1	12.5	0	0	0	0
	Multip.		11	7	63.6	3	21.3	1	9.1	0	0	0	0	0	0	0	0
30-34	Primip.	18		5	27.8	2	11.1	6	33.3	3	16.7	0	0	0	0	1	5.6
	Multip.		13	1	7.7	2	15.3	0	0	1	7.7	0	0	0	0	8	61.0
35-37	Primip.	61		16	26.7	19	31.1	12	19.7	6	9.8	6	9.8	0	0	2	3.3
	Multip.		55	38	44.9	8	9.5	6	7.1	1	1.2	0	0	1	1.2	2	2.4
38-44	Primip.	433		115	26.6	138	31.9	77	17.8	41	9.5	21	4.8	15	3.5	26	6.0
	Multip.		362	223	61.6	98	27.0	20	5.5	9	2.5	4	1.1	1	0.3	7	1.9
	Total	520	441														

MEANS IN HOURS

			SERIES	FENNING—MEMB. RUPT.	FENNING—NORMAL
38-44	Primip. 0-80 hr.	433	11.52 {11.1 s }	6.6	17.0
	Multip. 0-80 hr.	362	5.77 { 5.4 induction}	16.6	11.5

thirty hours. At term 88.6 per cent of the multiparas were dilated in ten hours or less and only 1.9 per cent were prolonged to more than thirty hours.

For comparison with Fenning's figures, the means in hours of the first stage, both with and without induction, are shown at the bottom of Table IV. As noted, Fenning's figures are calculated for three stages whereas those given for the present series are calculated for the first stage only.

We can deduce from Table IV that once labor is established, it proceeds with about uniform efficiency regardless of the period of gestation. However for some unexplained reason, 8 of the 13 multiparas in the thirty to thirty-four-week group had a first stage of over thirty hours.

TREATMENT

All patients with ruptured membranes are advised to enter the hospital even though pains have not started. It is generally believed that these patients will go into labor spontaneously within a few hours even if untreated, but that if labor does not begin the hazard to the mother and infant from infection increases in proportion to the lengthening of the time between the rupture of membranes and delivery.

Such patients are kept at bed rest in order to aid in preventing vaginal contamination and to prevent cord prolapse. The most critical time in regard to the latter would seem to be immediately after the rupture of membranes. This, however, usually occurs outside of the hospital and considerable activity on the part of the patient is necessary before admission is possible. Following admission, with patients who are otherwise normal, a general physical examination including a rectal examination is done. After a period of observation, a medical induction by means of castor oil and quinine or pituitrin is attempted if the patient does not go into labor spontaneously. If this treatment fails, further procedures depend on indications present in the individual case.

As previously noted, 182 patients in this series had inductions of labor. This group received 80 castor oil and quinine inductions, 119 pituitrin and 7 bag inductions (13 more Voorhees' bags were used but not for the sole purpose of induction). The percentage of failures among the combined castor oil and quinine and pituitrin inductions have been indicated in Fig. 3.

Of the 20 instances among the 1,000 cases in which Voorhees' bags were utilized, it was used for the single purpose of induction in 7 cases. Pituitrin inductions were simultaneously used so that it is difficult to evaluate the value of a bag induction alone. In two cases there was failure of induction and a craniotomy on a dead baby was done in one and a vaginal hysterotomy in the other.

The methods by which these patients were delivered is shown in Table V. Over half (55.5 per cent) were delivered naturally. The in-

TABLE V

MANAGEMENT	NUMBER	PER CENT	HOSPITAL	
Natural	535	53.5	59.21	C.L.I.H 15,957 cases 1934-1940
Low forceps	323	32.3	26.36	
Midforceps	38	3.8	3.81	
High forceps	1	0.1	-	
Version	11	1.1	0.98	
Dührssen's incisions	18	1.8	1.11	
Breech extraction	39	3.9	-	
Forceps aftercoming head	25	2.5	-	13,022 cases 1935-1940
Cesarean section	28	2.8	4.65	
Vaginal hysterotomy	1	2.1	0.03	
Radical cesarean section	2	0.2	0.28	
Craniotomy	8	0.8	0.38	
Manual removal placenta	34	3.4		

cidence of versions, midforceps, Dührssen's incisions, and radical cesarean sections is approximately the same as for the hospital generally, but an increase is noted in the incidence of outlet forceps and a decrease in the percentage of cesarean section. Probably the increase in the number of low forceps can be accounted for because of an increased concern for the mother or baby and a wish to terminate the labor as quickly as possible.

Seven of the 30 cesarean sections were performed on patients that had been, in general, under observation as outlined previously. One of the recognized contraindications to cesarean section at the Chicago Lying-in Hospital is the presence of ruptured membranes for over twenty-four hours, unless a radical section is to be done. These 7 patients had borderline indications for section, and if a trial of labor had been possible, this would have been given. However under the circumstances it was considered too hazardous to wait and the operation was performed immediately.

One of the radical cesarean sections was done because of prolonged membrane rupture, dystocia, and intrapartum infection. In the other inertia followed artificial rupture of the membranes and failed medical inductions which were undertaken because of a low-lying placenta. The latter was further indicated by the fact that sterilization had been previously advised.

In the entire group of 28 laparotrachelotomies, the operation was performed in 21 after the membranes had been ruptured for over six hours. Seven, or 25 per cent, became febrile; whereas the general morbidity rate in this hospital for cesarean section is 42.9 per cent.

MATERNAL MORBIDITY

The morbidity standard used at the Chicago Lying-in Hospital is that of the American Committee on Maternal Welfare, which considers all

TABLE VI. PUERPERIUM

MATERNAL MORBIDITY	NUMBER	PER CENT		C. L. I. HOSPITAL RATE
Total morbidity for this series	63	6.3		7.7 1932-1940
Nonoperative morbidity Membranes rupt 24 hr.+	8	6.4		
Morbidity etiology		CASES	SERIES	
Endometritis	28	44.4	2.8	
Wound infection	13	20.6	1.3	
Pyelitis	6	9.5	0.6	
Upper resp. infection	6	9.5	0.6	
Mastitis	4	6.0	0.4	
Thrombophlebitis	3	4.7	0.3	
Pulmonary embolism	2	3.2	0.2	
Maternal mortality Etiology: Eclampsia	1	0.1		1.75

patients as morbid who have a temperature of 38° C. or above on more than one day after delivery, excluding the first twenty-four hours. The morbidity in this series, the general hospital morbidity, and the separation of the febrile cases by causes are shown in Table VI. Of the total 63 cases which were febrile in the post-partum period, 41, or 65 per cent, occurred in patients that had had some type of operative procedure. Among the 80 nonoperative cases in this series with membranes ruptured over twenty-four hours, 6.4 per cent were febrile. This varies but slightly from the 6.3 per cent morbidity for the total 1,000 cases, and it is also less than the general hospital morbidity rate of 7.7 per cent.

There were 78 patients who had ruptured membranes plus a first stage totaling forty-eight hours and over. Of these, 8, or 10.25 per cent, became febrile. In 2 of the 8 cases, the cause of fever was extragenital; 1 patient had had Dührssen's incisions, and in 5 Voorhees' bags had been inserted.

A diagnosis of intrapartum infection was made prior to delivery on 6 of these patients. Two were at term. One was delivered by a successful radical cesarean section, and in the other the infection subsided in a few days following delivery by a craniotomy on a dead baby. (The baby showed intrauterine pneumonia.) The other two intrapartum infections followed unsuccessful attempts to induce labor with pituitrin and Voorhees' bags at twenty-four and thirty-three weeks' gestation, respectively. A craniotomy was done to deliver one patient and a vaginal hysterotomy to deliver the other. One developed septicemia and the other a pelvic thrombophlebitis with pulmonary infarction. Both patients recovered after a prolonged convalescence.

In retrospect, it is believed that abdominal hysterotomy would have been the method of choice in the two last cases. The high degree of uterine inertia which has been demonstrated at these periods of gestation should cause us to anticipate failure of induction in a high percentage of cases.

In addition there were two patients who had an elevation of temperature during labor who were afebrile after delivery.

MATERNAL MORTALITY

One patient in this series, who had had no prenatal care, died. She entered the hospital in coma, with premature detachment of the placenta and anuria. The membranes were ruptured artificially to induce labor. She delivered within a short period but subsequently died. Autopsy showed changes in the liver and kidneys consistent with eclampsia.

FETAL MORTALITY

The mortality among the offspring of women with premature rupture of membranes was 5.4 per cent. The total fetal and neonatal mortality at the new Chicago Lying-in Hospital, since it opened in 1931, is 4.37 per cent. In the present series, as well as in the total hospital mortality, all fetuses beyond twenty-two weeks' gestation are included.

In 17.4 per cent of the cases in this series, delivery took place prior to the thirty-eighth week. Infants delivered in the same period in the total hospital series amounted to only 6.7 per cent. The mortality rate (stillbirth and neonatal deaths) for our institution shows approximately 21 times as great a mortality when delivery occurs before the thirty-eighth week as after that time. The expected mortality in the cases included in the present study would be 9.9 per cent if the same mortality rates held for term and premature infants as exist in the total deliveries. There is, therefore, actually less than the expected mortality.

The mortality rates for the previable, premature, and term infants are shown in Table VII both in percentage of deliveries and in rates per 1,000 live births. When the death rates are calculated per 1,000 live births, the total hospital previable and premature rates are considerably less than those in the group with premature rupture of the membranes, while the rate for those at term is slightly more. This is probably accounted for by the much greater proportion of mature infants among general hospital admissions.

TABLE VII. FETAL MORTALITY

	PREMATURE RUPTURE MEMBRANES			HOSPITAL
FETAL AGE	DELIVERIES	DEATHS	PER CENT	PER CENT
Previable	16	15	93.7	96.61
Premature	158	25	15.8	32.66
Term	826	14	1.69	1.93

Mortality Rates Per 1000 Live Births

	PREMATURE RUPTURE OF MEMBRANES		HOSPITAL	
FETAL AGE	STILLBIRTHS	NEONATAL	STILLBIRTHS	NEONATAL
Previable	7.19	8.21	2.9	2.8
Premature	12.32	13.34	9.24	10.89
Term	9.24	5.13	10.89	7.07

Although the percentage mortality of the previable group should theoretically be 100 per cent, one infant survived in this group and was discharged from the hospital on the eightieth day. Subsequently it developed gliomas of the eyes and has probably since died, although this information is not available at the present time.

The reason for the seemingly high percentage of survival among the premature infants with prematurely ruptured membranes compared with the general hospital rate (15.8 per cent mortality and 32.66 per cent for the hospital) is obscure, although labor is shorter on an average than when membranes are not ruptured. Perhaps it is safe to assume that the fetal mortality rate was generally not increased by the fact that the membranes were ruptured prematurely.

The mortality percentages for the two groups vary but little at term, although here again those with premature rupture have a slightly lower death rate (1.69 per cent) than those in the general hospital group (1.93 per cent).

One of the most surprising findings in relation to mortality is that, although patients at or past forty weeks rarely fail to go rather promptly into labor following rupture of membranes, the mortality is very high among those infants who are delivered after a latent period of fifty-five hours or more (Fig. 1). Of 8 such infants four died, and all of the deaths were due to pneumonia. In association with the delivery of one there had been a prolonged first stage. Only one previable infant of the 15 examined at autopsy showed any evidence of intrauterine lung infection, although in 42.3 per cent of all the deliveries between twenty-two and twenty-nine weeks, membranes had been ruptured for over one hundred hours. Another infant from this group died of aspiration pneumonia at seventy days of age. This is in marked contrast with the infants at term where the findings are as above noted. One might theorize that previable infants do not breathe in utero, that they rarely do before forty weeks, and frequently do thereafter. See Fig. 1 for case distribution of pneumonias.

Among the 52 infants subjected to autopsy, 6 showed major malformations, 4 intracranial hemorrhages, and 2 erythroblastosis; 5 showed the petechial hemorrhages usually associated with intrauterine asphyxia. In 11 infants and fetuses, there was an inflammatory exudate in the lungs. This was associated with intracranial hemorrhage in one instance and with cardiac malformations in two instances.

Among 2,000 autopsies performed at the Chicago Lying-in Hospital on fetuses and newborn infants, pneumonia, as the only pathologic lesion, was found in 7.9 per cent of the autopsies and in an additional 3.8 per cent as a contributing cause. This is a total of 11.6 per cent which is considerably lower than the 21.2 per cent (11 in 52) found in this series.

CONCLUSIONS

1. The uterine musculature shows a progressively increasing degree of resistance to medical or mechanical induction of labor prior to term, reaching a high degree of inertia between twenty-two and thirty weeks. Vaginal or abdominal hysterotomy suggest themselves as being the safest primary termination of pregnancy at this stage.

2. There is a low maternal morbidity among patients treated conservatively with prolonged membrane rupture.

3. Because of the possibility that the patient may be in painless labor, medical induction of labor at term with membranes ruptured should be delayed ten to fifteen hours if possible.

4. There is a high fetal mortality from pneumonia among infants at forty or more weeks of gestation where the membranes have been ruptured for over fifty-five hours.

5. Based on comparative statistics, premature rupture of the membranes does not appear to be followed by an increased mortality or morbidity rate despite the increased number of operative deliveries.

DISCUSSION

DR. E. D. PLASS, IOWA CITY, IOWA.—Having already been the recipient of much unfavorable criticism because of my advocacy of premature rupture of the membranes as a means of inducing labor in indicated cases and of my extensive use of premature elective rupture on an economic and convenience basis alone, I accepted the invitation to discuss this paper with some trepidation. My acceptance was dictated largely by the desire to restate my position which has, I fear been somewhat distorted by the opponents of elective rupture. I have never, I think, taken any other position than that "The induction of labor by premature rupture of the membranes after stimulation of the uterus through the action of castor oil, quinine, and pituitary extract is safer than the other forms of mechanical irritation employed for this purpose (bougies, bags, or packing)." There has been no reason to alter this position, although it has been recognized that the procedure is not adaptable to very immature pregnancies, where some form of hysterotomy is to be preferred.

I have nowhere advocated routine elective induction of labor by this means, even though our own experience has been so satisfactory that we have continued its use even after the original experimental series were completed. Under the conditions obtaining in our own clinic with the large majority of patients coming from some distance and being supported by public funds, elective rupture becomes a social and economic question, provided only that it does not adversely affect the outcome for mother or child. By inducing labor at the calculated date when the fetus is evidently mature, it is possible to return the mother to her home a few days earlier than otherwise and thus to restore the continuity of family life, and to reduce somewhat the expenditure of state money. Other clinics and individuals must necessarily determine their attitudes according to the conditions under which they operate.

The series of cases presented by Dr. Morton largely confirms our earlier compilations and reinforces our conclusions that certain advantages apparent in labor following premature rupture of the membranes counterbalance other risks evidently connected directly with the early loss of amniotic fluid. The danger of, and practical impossibility of anticipating, a prolonged latent period argues against the method, but in both Dr. Morton's experience and in ours, this risk is not excessive and is surely justifiable at least when the induction is indicated.

The authors are evidently not enthusiastic about elective rupture, and I shall certainly not argue the point with them, but their results indicate that premature rupture of the membranes is at least not the dangerous complication which some would have it.

DR. L. W. MASON, DENVER, COLO.—After I began the practice of medicine about fifteen years ago, several incidents happened which made me wonder if what I had been taught about premature rupture of the membranes was true. At first when patients would call during the night to tell me that their membranes had ruptured, bearing in mind what I had learned that premature rupture resulted in a prolonged, inefficient, and ineffective labor, I would tell these patients to go to the hospital and I would see them the next morning. Usually the intern would call within the next three or four hours to tell me to hurry over, and frequently I did not get there in time to deliver even the placenta.

I formerly studied 1,000 cases at the University of Colorado School of Medicine, with results very similar to those reported by Dr. Morton and Dr. Plass. This material was written up and submitted in 1933 to the *Journal of the American Medical Association*. It was promptly rejected for the reason that my conclusions were contrary to current practice. These conclusions, of course, were only inescapable facts brought out by the study. About six months ago, an article was published in that Journal entitled "Changing Concepts of Dry Labor."

Previous to 1933, two papers had come to my attention, one by Schultz, of California, a study of spontaneous rupture of the membranes, and the other by Guttmacher and Douglas of Johns Hopkins, a report of the rupture of the membranes for the induction of labor. The results of all of these studies to date have been substantially the same. I found in my own series that the total average time in labor was reduced by about 60 per cent, both in primiparas and multiparas. There was no demonstrable increase in infant or maternal morbidity or mortality. Factors which prolong labor in cases in which the membranes had ruptured before complete dilatation of the cervix were found to be unrelated to the presence or absence of the intact membranes.

A factor which I think sometimes results in a long latent period after rupture of the membranes is that all the amniotic fluid is not out. In rupturing the membranes for the induction of labor one should attempt to rock the head back several times to insure that all the amniotic fluid, and not merely the forewaters, drains away. Otherwise we may have a condition that sometimes happens with slight spontaneous rupture, when the fluid may dribble away for a week or two before the onset of labor.

DR. J. W. REDDOCH, NEW ORLEANS, LA.—Since the original report of Drs. Guttmacher and Douglas we have used rather routinely artificial rupture of the membranes for induction of labor on our service at the Charity Hospital. One of our special problems is that many of our patients come in for hospitalization three or four weeks before the expected onset of labor. With this number of cases we have a fertile field for study of artificial rupture of the membranes.

The results of our studies have paralleled those of Dr. Plass. A few years ago I reviewed the first 100 cases in which there were two fetal deaths, both due to prolapse of the umbilical cord. Since then we have put the patient on her feet after rupturing the membranes and have had no more trouble with this complication. We have selected vertex cases only, in which the cervix was not thicker than three-fourths of an inch whether multipara or primipara. We have not chosen cases in which the head was above the pelvic brim.

DR. MORTON (closing).—I can assure Dr. Plass that no effort was made to have an editorial policy in this study of artificial rupture of the membranes. This series included patients who had both spontaneous and artificial rupture of the membranes.

A STUDY OF ONE HUNDRED AND FIFTEEN CASES OF RUPTURED ECTOPIC PREGNANCY*

W. O. JOHNSON, M.D., F.A.C.S., LOUISVILLE, KY.

(From the Department of Gynecology, University of Louisville Medical School)

PROBABLY since the inception of conception woman has been subject to ectopic pregnancy. The first record of such a case was in 1050 A.D., but not until December, 1859, was the first surgical treatment carried out by Dr. John Bard of New York. Lawson Tait, in 1883, published the first successful series of operated cases.

We do not choose to re-state the numerous causes advanced for the production of ectopic pregnancy, but the most prominent and consistent factor appears to be the result of infection. Authorities on veterinary obstetrics say domestic animals are relatively free from infection and deformities. Dr. W. L. Williams,[13] emeritus professor of veterinary obstetrics, Cornell University, states: "A careful search of veterinary literature fails to reveal apparently authentic cases of tubal pregnancy in domestic animals. The few actual cases of extrauterine pregnancy reported have been due to rupture of the uterus, most of which result from torsion of the uterus."

Dr. G. Fleming[15] gives as his reasons for the infrequency of extrauterine pregnancies in animals:

1. Different disposition of their generative apparatus.
2. A lesser tendency of domestic animals to disease, functional disorders, and deformities.
3. Their function being only that of reproduction.
4. Ectopic pregnancy apparently is no more common in multiparas than uniparas, nor in any one species.
5. No report has been made concerning *Brucella abortus* and ectopic pregnancy.

From the above it seems that low incidence of infection, freedom from functional diseases and deformities, and exclusive use of sex organs for reproduction do play a part in the freedom from ectopic pregnancy. If this is true, we should endeavor to point out means of correction, and have more detailed studies of the cases.

At present there is no pathognomonic sign or symptom. A diagnosis rests upon a good clinical history associated with other clinical signs in an ectopic-minded physician. We are presented with ectopic pregnancy in one of three phases: (1) emergency, (2) state of deliberation, and (3) obscurity. In each of these phases our method of treatment differs.

*Presented at the Thirteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, New Orleans, La., October 2 to 4, 1941.

We herewith present a series of 115 cases of ruptured ectopic pregnancy treated in the Gynecological Department of the Louisville City Hospital, from July 1, 1927, to January 1, 1941. Each case was confirmed by pathologic report of the specimen removed. There were 27 additional cases in which unconfirmed diagnosis of ectopic pregnancy was made, which are not included in this series.

The only constant factor in ectopic pregnancy is inconsistency.

For a more detailed study, these 115 cases have been divided clinically into three groups (Table I).

TABLE I. CLINICAL GROUPING OF 115 CASES OF RUPTURED ECTOPIC PREGNANCY

GROUP		CASES	PER CENT
I	Patients with signs of internal hemorrhage, in whom prompt operation was imperative	62	53.8
II	Patients in whom internal bleeding had stopped; surgery was instituted when patient's condition warranted	35	30.4
III	Obscure cases of long-standing, in which hemorrhage and product of conception were encapsulated	18	15.6
	Total	115	99.8

Chart 1 gives the incidence of cases by years in the Louisville City Hospital. Two peaks appear which are not explained by the progressively increasing number of patients hospitalized. This gives an average incidence of 1 ectopic pregnancy in 137 deliveries in the City Hospital.

Over a period of five years in five private hospitals very little change is noted in the number of ectopic pregnancies cared for, in spite of increasing number of hospital deliveries. These hospitals admit only white patients and draw their cases from industrial and farming districts. In private hospitals the rate is one ectopic pregnancy to 78.5 deliveries (Chart 2). Note that the ratio of increase of ectopic pregnancy is greater in the City Hospital in spite of the increasing number of deliveries, while the yearly ratio remains more constant in the private hospitals in spite of increased deliveries. While most patients with ectopic pregnancies are hospitalized, a majority of abortions and deliveries are cared for in the home, and a true ratio of ectopic to normal pregnancies and abortions can scarcely be obtained. The cause for fluctuations in cases of ectopic pregnancy remains to be determined. The determination is dependent upon an accurate recording of our findings as an important cause of fetal and maternal deaths; we should insist that our vital statistics include incidence and causes of ectopic pregnancies.

Infection appears to be the dominating factor. Twenty-two per cent of our series had a definite history of previous infection before the ectopic pregnancy occurred. In the 115 cases, only 50 colored patients, and 33.3 per cent, had a positive Wassermann or history of syphilis.

One might expect a higher incidence of ectopic pregnancies in the colored race.

Cauterization of the cervix or tubal insufflation after an old pelvic inflammatory process is a rarely emphasized source of ectopic pregnancy.

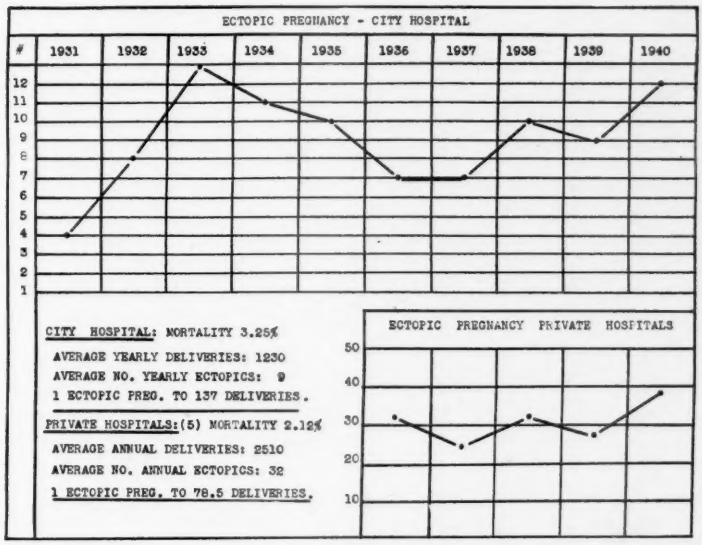
ECTOPIC PREGNANCY - CITY HOSPITAL
1931 1932 1933 1934 1935 1936 1937 1938 1939 1940
12 11 10 9 8 7 6 5 4 3 2 1
CITY HOSPITAL: MORTALITY 3.25%
AVERAGE YEARLY DELIVERIES: 1230
AVERAGE NO. YEARLY ECTOPICS: 9
1 ECTOPIC PREG. TO 137 DELIVERIES.
PRIVATE HOSPITALS:(5) MORTALITY 2.12%
AVERAGE ANNUAL DELIVERIES: 2510
AVERAGE NO. ANNUAL ECTOPICS: 32
1 ECTOPIC PREG. TO 78.5 DELIVERIES.
ECTOPIC PREGNANCY PRIVATE HOSPITALS
50 40 30 20 10

Chart 1.

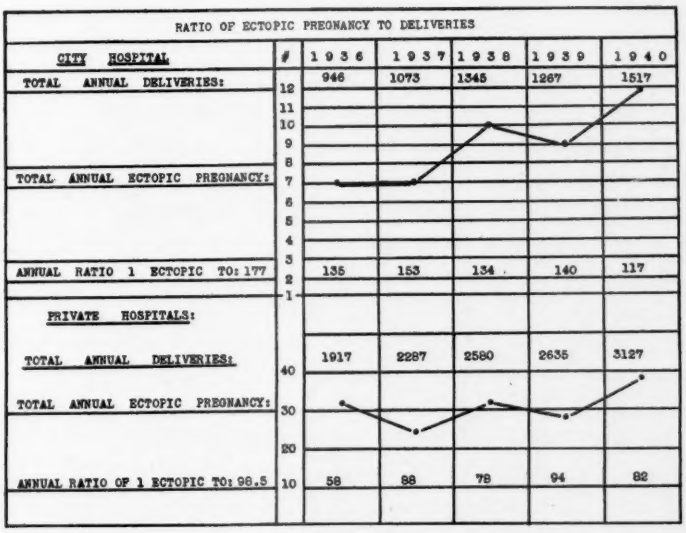
RATIO OF ECTOPIC PREGNANCY TO DELIVERIES
CITY HOSPITAL
1936 1937 1938 1939 1940
TOTAL ANNUAL DELIVERIES: 946 1073 1345 1267 1517
TOTAL ANNUAL ECTOPIC PREGNANCY:
ANNUAL RATIO 1 ECTOPIC TO: 177 135 153 134 140 117
PRIVATE HOSPITALS:
TOTAL ANNUAL DELIVERIES: 1917 2287 2580 2635 3127
TOTAL ANNUAL ECTOPIC PREGNANCY:
ANNUAL RATIO OF 1 ECTOPIC TO: 98.5 58 88 78 94 82
12 11 10 9 8 7 6 5 4 3 2 1
40 30 20 10

Chart 2.

In this series, 18 per cent of cases had abortions before the ectopic pregnancy; in 8.6 per cent the ectopic was the first pregnancy.

Hypoendocrine factors obviously seem to be very important causative agents, but very little evidence has been produced. Could not inade-

quately developed tubes and uteri, or inadequate circulation be as potent factors in the production of such a catastrophy as pelvic infections? Are not prolonged periods of infertility frequently the result of endocrine imbalance? May not the loss of cilia action, or absence of peristaltic motions or tubes weaken, impede, or even destroy the ingress of spermatozoa for fertilization just as readily as infection?

Endometriosis has been given as a causative factor in ectopic pregnancy. Fortunately, or unfortunately, patients with endometriosis are relatively infertile. No cases of endometriosis were noted in this series.

There were 65 white and 50 colored patients; the average age of the group was 29 years. The average age in the more acute group was six years younger than in the obscure group. Youngest case was 17 years, oldest 43.

In Group I, there were 10 cases of ectopic pregnancy as a first pregnancy. Eight patients had been married less than two years.

The age incidence by decades was as follows (Table II):

TABLE II. AGE INCIDENCE

AGE—YEARS	CASES	PER CENT	
14-20	10	8.6	
20-30	65	57.0	87%
30-40	35	30.0	
40-	5	4.3	

Eighty-seven per cent of all the cases of ectopic pregnancies occurred between twenty and forty years of age. Seventy-eight per cent of all patients were multiparas with an average of 2.7 children. Five patients were married twice with pregnancies in both marriages. This points to different etiologic factors. Twenty-four patients miscarried previous to the ectopic pregnancy.

Long periods of infertility have often been listed as an etiologic factor in ectopic pregnancy. The average interval between gestations was 4.8 years (as well as could be ascertained). There were two patients with 18-year intervals; one, 16 years; three, 11 years; and three, 10 years from the previous gestation. A question of general interest would be: Were these periods of apparent infertility due to inadequate glandular function, infection, contraception, or general debility on the part of one or both partners? Can all this be explained by infections?

Over 83⅓ per cent of the patients had normal menstrual periods (Table III). Eleven in Group I had no period of amenorrhea. On careful study of these cases one might have found the last regular menstrual period was either abnormally short, scant, or delayed beyond the usual time. Such a history is especially important in clinching the diagnosis. The average duration of amenorrhea was less than three months in all cases; longest history was 6.5 months for an abdominal pregnancy.

TABLE III. MENSTRUAL CHANGES AND GESTATIONS

GROUP	TYPE OF MENSES	PERIOD OF AMENORRHEA	DURATION OF ABNORMAL BLEEDING	AVERAGE NO. OF PREGNANCIES AND ABORTIONS	INFERTILE
I	Regular, average duration 4 days: 47 patients Irregular, average duration 6 days: 15 patients	11, no menstrual changes Average: 1 Mo. 18 days	11 had no abnormal bleeding Average: 9 days	10 cases first pregnancy Average 2.8 pregnancies 14 abortions	Three patients: 11 yr. Three patients over 10 yr. Average: 3.2 yr.
II	Regular, average duration 4.5 days: 31 patients Irregular, average duration 5.1 days: 4 patients	Average: 2 Mo. and 4 days	7 had no abnormal bleeding Average: 20 days	Average 2.8 pregnancies 7 abortions	
III	Regular, average duration 3.5 days: 16 patients Irregular, average duration 4 days: 2 patients	Average: 2 Mo. and 13 days	5 had no abnormal bleeding Average: 17 days	Average 2.4 pregnancies 6 abortions	Two patients: 18 yr. Average: 4.8 yr.

Pain, of which there are at least five different types, was present in our cases, 91 per cent giving pain as their chief complaint, and most constant symptom. Fifty per cent of the pain was cramp-like in character (Table IV).

In Group I, the pain was more often sharp and stabbing. When this type of pain, radiating to the rectum (so-called "bath-room sign") was associated with collapse, it was of the greatest significance. Rigidity of abdomen was unusual in these cases, in contrast to the abdomen of infection.

Vaginal bleeding occurred in 60 per cent of cases as the chief complaint in the acute group, and in 50 per cent of the obscure cases. Nausea, vomiting, dysuria, and urinary frequency occurred in over 50 per cent of the acute cases, to lesser degree in the more obscure cases where the peritoneal irritation had begun to subside.

The pelvic finding, in about 50 per cent of the cases, was a mass in the posterior cul-de-sac. In the majority of instances the mass in the side was fairly frequently associated with the side in which the pain was greater, and as frequently located in right as in left side.

Comparison of the three groups shows greatest increase in symptoms of Group I over Group III, especially in abdominal tenderness and distention, with 32.5 per cent of cases showing shifting dullness in acute cases.

The laboratory findings (Table V) show a definite anemia in all groups, with leucocytosis in Groups I and II, but not much variation in differential count. Urine examinations, in the majority of instances, were normal.

TABLE IV. CLINICAL FINDINGS

GROUP	CHIEF COMPLAINT		SYMPTOMS		PELVIC FINDINGS	
I	Abdominal pain:		Vaginal bleeding	38—60.8%	Pelvic mass:	
	R. L. Q.	25—40.3%	Leucorrhea	32—51.7%	R. L. Q.	20—32.2%
	L. L. Q.	17—27.4%	Vomiting	38—60.8%	L. L. Q	15—24.1%
	Both L. Q.	20—32.2%	Nausea	15—24.2%	Posterior	27—43.5%
	Vaginal bleeding	37—60.0%	Dysuria, frequency	12—19.5%	Soft cervix	35—56.8%
	Abdominal tumor	2—3.0%	Weakness	13—20.0%	General abdominal tenderness	56—91.0%
			Fainting	11—18.7%	Abdominal distention	47—77.2%
			Shoulder pains	9—15.0%	Shifting dullness	20—32.5%
			Dyspnea	6—10.0%	Shock	12—19.3%
62					Enlarged uterus	27—43.0%
II	Abdominal pain:		Vaginal bleeding	21—60.2%	Pelvic mass:	
	R. L. Q.	12—34.2%	Leucorrhea	20—56.0%	R. L. Q.	9—25.7%
	L. L. Q.	10—28.5%	Nausea	22—62.4%	L. L. Q.	11—31.4%
	Both L. Q.	13—37.1%	Vomiting	19—54.1%	Posterior	15—43.8%
	Vaginal bleeding	23—66.0%	Dysuria, frequency	11—30.0%	Soft cervix	14—41.0%
	Abdominal tumor	2—5.7%	Breast changes	7—20.3%	General abdominal tenderness	23—67.0%
			Weakness	24—73.0%	Abdominal distention	13—36.0%
					Enlarged uterus	26—74.5%
					Bloody vaginal discharge	15—41.6%
35						
III	Abdominal pain:		Vaginal bleeding	10—58.0%	Pelvic mass:	
	R. L. Q.	7—38.8%	Leucorrhea	9—50.0%	R. L. Q.	5—27.7%
	L. L. Q.	3—16.6%	Nausea	5—25.0%	L. L. Q.	3—16.6%
	Both L. Q.	8—44.4%	Vomiting	6—33.0%	Posterior	10—55.5%
	Vaginal bleeding	9—50.0%	Frequency	3—16.6%	Soft cervix	10—55.5%
	Abdominal tumor	2—11.1%	Weakness	2—10.0%	Enlarged uterus	9—50.0%
					General abdominal tenderness	10—55.5%
					Abdominal pregnancy	2—11.1%
18						

The most informative study is that of admission temperature, blood pressure, and pulse rate. In Group I, there was found an average rise of more than 25 points in pulse rate, with a fall of more than 27 points in systolic blood pressure. Thirty-six per cent of Group I had subnormal temperature or were in shock upon admission.

Our attitude toward laboratory procedures, used as diagnostic aids in this group, is that while the Aschheim-Zondek or Friedman tests may be confirmatory of a pregnancy, they are not a constant aid for they remain positive only as long as the fetal cells secrete hormone into the maternal blood, and twelve hours is the shortest period of time in which an accurate reading can be obtained. Many of the patients with severe cases would have died unless immediate treatment had been instituted. Falls-Freda and Cohen colostrum pregnancy test may develop to be of

TABLE V-A. LABORATORY FINDINGS

GROUP	R. B. C.	W. B. C.	HEMOGLOBIN	P. M. N.	SEDIMENTATION
I	Average 2,937,000	Average 10,654	Average 8.4 Gm. (Sahli)	Average 78%	27 Cases (68% Negative)
II	Average 3,523,119	Average 9,803	Average 10.5 Gm. (Sahli)	Average 73%	18
III	Average 3,966,080	Average 6,825	Average 10.9 Gm. (Sahli)	Average 72%	15

TABLE V-B. LABORATORY FINDINGS

GROUP	WASSERMANN	ASCHHEIM-ZONDEK	BLOOD PRESSURE	PULSE	P. O. TEMP. RISE
I 62	18% of all white cases were positive	15 2 Positive	91/60	100	101.4° F. Normal in 4.5 days
II 35		11 (All negative)	110/72	98	100.2° F. Normal in 4.5 days
III 18	33% of all colored cases were positive	6 (All negative)	118/75	90	100.4° F. Normal in 6 days

great benefit in excluding abdominal infection and other interperitoneal hemorrhages. In doubtful cases, a positive Aschheim-Zondek test strongly suggests the presence of pregnancy; negative, not always true. In face of a positive Aschheim-Zondek one must be cautious.

A positive, delayed, direct van den Bergh reaction is of help in that it indicates the presence of free blood in the abdominal cavity.

Diagnostic posterior colpotomy with aspiration of fluid may be of help; it was helpful in 6 cases of our series.

Sedimentation tests were run in one-third of the cases, and were sixty minutes or over, which is well within normal range. Only 8 per cent of these cases having sedimentation tests were abnormal, and these were associated with pelvic infections. Sedimentation test is not of importance in differentiating inflammation from ectopic pregnancies.

Hysterosalpingography is an adjunct in the more obscure cases, where patient is not too ill for the procedure and infection not present; and is excellent in differentiation of rupture of follicle cyst with bleeding and ectopic pregnancy.

We wish to emphasize some of the rather frequent clinical findings, which are not usually emphasized in this type of case:

1. Softening of the cervix occurs in over 50 per cent of the cases, and exquisite sensitivity of the cervix to motion is a very important finding. This is due to changes associated with pregnancy and the

peritoneal irritation from the blood gravitating from the ends of the tubes, or ruptured tubal walls, into the cul-de-sac, affecting the utero-sacral ligaments, resulting in pain on motion.

2. Enlargement of the uterus, general abdominal tenderness and distention without rigidity, with unilateral mass in 50 per cent of cases.

3. Low or subnormal temperature and progressive anemia with leucocytosis.

4. Unilateral pulsation of the uterine artery frequently found. The uterus is usually displaced downward and making it more accessible to the examining finger, with sudden, excessive demand for blood supply increases the activity of the artery on the affected side.

For a woman of childbearing age, the association of a previously abnormal period, or period of amenorrhea with abdominal pain or abnormal bleeding should always bring to mind the possibility of ectopic pregnancy. *Remain ectopic-minded.*

Ectopic pregnancy warrants operation when diagnosis is made. There is no conservative treatment for ectopic pregnancy. In my opinion, it is better to make the mistake of opening an abdomen of questionably early pelvic inflammatory disease than to have a death from hemorrhage with ectopic pregnancy.

TABLE VI

GROUP	SURGERY		PATHOLOGY		RESULTS
I	Salpingectomy		Ectopic pregnancy	100.0%	1 Dead, pneumonia four days post-operative
	Right	21—33.9%	Salpingitis, chronic	8—13.0%	
62	Left	25—40.3%	Ovarian cyst	2— 3.2%	
	Bilateral	6— 9.6%			
	Oophorectomy	4— 6.4%			
	Appendectomy	5— 8.0%			
	Transfusion	21—33.9%			
	Autohemotransfusion	17—27.4%			
II	Salpingectomy		Ectopic pregnancy	100.0%	1 Dead, concealed hemorrhage 1 Dead, peritonitis
	Right	21—60.0%	Salpingitis, chronic	6—17.1%	
35	Left	7—20.0%	Oophoritis	1— 2.8%	
	Bilateral	7—20.0%	Uterine fibroids	2— 5.7%	
	Oophorectomy	3— 8.5%	Abdominal pregnancy	3— 8.5%	
	Appendectomy	15—42.8%			
	Fundic Hysterectomy	4—11.4%			
	Autohemotransfusion	7—20.0%			
III	Salpingectomy		Ectopic pregnancy	100.0%	1 Dead, shock and hemorrhage postoperative Mortality 3.05%
	Right	3—16.6%	Salpingitis, chronic	6—33.3%	
18	Left	2—11.1%	Oophoritis	2—11.1%	
	Bilateral	13—72.2%	Abdominal pregnancy	2—11.1%	
	Oophorectomy	5—27.7%			
	Appendectomy	14—77.7%			
	Hysterectomy	9—50.0%			
	Transfusion	6—33.3%			

The types of surgery are quite different in the three groups (Table VI). In the acute group, a greater number of autohemotransfusions and transfusions are carried out, 40 per cent being transfused either before or during the operation.

Seventy-three per cent of acute cases had unilateral salpingectomy without hysterectomy. This is done only as a life-saving measure. We

do not advocate converting acute cases into chronic cases so that more deliberation can be carried out, but recommend the minimum curative surgery.

In Group II there were 80 per cent unilateral salpingectomies with 11 per cent hysterectomies, and fewer transfusions. In this group the patient could be better prepared for operation.

Group III had 27 per cent unilateral salpingectomies and 50 per cent hysterectomies. This was a correction of the pathology at hand for permanency of results in patients properly prepared.

Such an attitude necessitates the separation of ectopic pregnancy into groups, and reveals why different types of surgery are done in ectopic pregnancy.

The average time of operation in Group I was fifty-five minutes, the shortest twenty-five minutes; in Group II, eighty-eight minutes; and in Group III, ninety-five minutes. Time is indeed a factor in the handling of these severely shocked patients, and it is important to reckon with it.

Anesthesia is also important. In our cases either local, or carefully administered cyclopropane anesthesia was given.

Patient's hospitalization averaged 18.5 days; 30 per cent of the patients remained in the hospital over twenty-one days.

Correct diagnosis preoperatively was made in 71 per cent of cases in Group I, 48 per cent of cases in Group II, and 16 per cent of cases in Group III.

In this series there were five abdominal pregnancies, the result of tubal abortions. The oldest was apparently a six months' gestation. In all of these the products of conception were nonviable before operation was performed.

There were four deaths: one in Group I from pneumonia, two in Group II from concealed hemorrhage and peritonitis, and one in Group III from shock and hemorrhage, giving a mortality rate of 3.05 per cent.

In postoperative follow-up an average of two visits in three months show 13.3 per cent had increase in vaginal discharge, with 5 per cent having increase in menstrual pain. In all cases where the uterus was not removed, menstrual function had returned.

Prompt, conservative surgery, transfusions, and postoperative supportive treatment will miraculously transform a desperate case to one with a relatively smooth convalescence in a short period of time.

SUMMARY

1. Presentation of 115 cases of ruptured ectopic pregnancy, giving the incidence and comparison with private hospitals, and the ratio of ectopic pregnancies to births in the city and private hospitals.

2. Division of cases into three groups (I. acute emergencies, II. deliberate surgery, III. obscure cases) with comparison of the clinical findings, as to age, race, clinical symptoms, physical and laboratory

findings, showing that there is a difference in the three groups, and a necessity for differentiation in the type of treatment.

3. Emphasizing that careful history and summary of clinical findings, varied types of pain, subnormal temperature, abdominal distention without rigidity, soft cervix, enlarged uterus, and leucocytosis in a woman of the childbearing age should keep one "ectopic-minded."

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DISCUSSION

DR. HILLIARD E. MILLER, NEW ORLEANS, LA.—Dr. Johnson's study of 115 cases of ectopic pregnancy from a public institution in Louisville suggests some interesting comparisons with a similar study of 137 cases which I made last year from Touro Infirmary, a private institution in New Orleans. The age range in both series was the same, 17 to 43 years, and in both the highest incidence occurred in the period between 20 and 40 years. In both series the mortality was unusually low, 3.05 per cent in Dr. Johnson's series from the public hospital, and 2.18 per cent in my own from a private institution, where, as would naturally be expected, patients are seen earlier and in better condition.

In both series the great majority of patients complained of pain, which was of several different kinds. Pain is, however, a symptom common to a great many diseases and far more valuable from the standpoint of diagnosis is the history of any sort of menstrual irregularity. Frank amenorrhea was present in more than half the cases in my series, and in one-sixth of the patients in Dr. Johnson's series. Four-fifths of the patients in my series, however, presented a history of irregular bleeding, irregular in relation to the normal time of the period and atypical in relation to the type of bleeding. The abnormally dark color of the discharge is characteristic. When the history is being taken in a case in which one suspects ectopic pregnancy, the questioning should be detailed on these various points. A simple inquiry as to whether a period has been skipped is not sufficient, and the usual patient will not supply the additional details unless she is specifically asked about them.

From the standpoint of physical findings, tenderness, which is present in most cases, and rigidity, which is present in a fair number, are no more useful per se from the standpoint of diagnosis than is pain. On the other hand, the finding of a mass either by abdominal or by pelvic examination is important, and sensitivity of the cervix on motion is present in perhaps half of all cases; I am inclined to regard this finding as almost pathognomonic, though its absence, of course, is not significant.

Though aware that a physician who uses the words "always" and "never" is looking for trouble, I nonetheless am willing to make the unqualified statement that the treatment of ectopic pregnancy is surgical, and that surgery should be performed as soon as the diagnosis is made. I am not in favor of delaying operation for any reason at all. It is quite true that in many instances delay does no harm, but there is no way of determining the cases in which it will do no harm as distinguished from those in which it will do a great deal. Even though the patient is in shock, operation should still be carried out without delay. The shock is due to hemorrhage, and its logical treatment is the control of hemorrhage. Opening the abdomen and tying off the bleeding vessel or removing the tube, if carried out gently and rapidly, under light anesthesia, does not add to the shock. Adjuvant measures, such as infusion, or preferably, transfusion, can be carried out equally easily and far more profitably in the operating room, while the fundamental trouble is being corrected.

The clear-cut case of ectopic pregnancy is so obvious that the diagnosis can scarcely be missed. The obscure case can furnish as difficult a problem as any phase of gynecology. If the confusion is with another condition for which immediate surgery would be demanded, as for instance appendicitis, there is really no problem, for one merely operates at once, with the acute condition in the abdomen as the general background. If the confusion is with a condition for which emergency surgery is unnecessary or is actually undesirable, the problem is less simple, though my own opinion is still that if the mere suspicion of ectopic pregnancy exists, no time should be wasted on refinements of diagnosis. Less harm is done by opening the abdomen in pelvic inflammatory disease than by withholding it in possible ectopic pregnancy. Furthermore, if definite diagnosis is impossible, I should personally prefer exploratory laparotomy to either of the diagnostic methods suggested by Dr. Johnson. I have no doubt that colpotomy and hysterosalpingography both yield useful information, but I question whether it is worth the additional risk both methods seem to introduce.

I also take issue with Dr. Johnson as to the performance of any type of hysterectomy in ectopic pregnancy, except on indications for which the uterus would be removed under any circumstances, and with the further provision that the patient's condition warrants the additional surgery. The object of hysterectomy, as Dr. Johnson states, is to insure permanent results, in other words to guard against recurrence. In my own series of 137 cases there were 5 recurrences, 3.6 per cent, which, curiously, is exactly the incidence of recurrence reported by Smith in a collected series of 1,608 cases of ectopic pregnancy.

I grant the risk, actual and potential, of ectopic pregnancy, but I still question whether a risk of recurrence of less than 4 per cent justifies the sterilization of a woman in the child-bearing years, particularly if she has no other living children. If Dr. Johnson has the figures available, I hope he will mention the percentage of recurrence in his series. I should also like to know the age and race of the women submitted to this radical procedure, both of which, of course, may throw a very different light upon the matter.

DR. WILLIAM D. PHILLIPS, NEW ORLEANS, LA.—A rather unique experience of a few days ago brought out one point which I have not heard mentioned, namely the extreme leucocytosis in acute rupture of an extrauterine pregnancy. I would like to ask Dr. Johnson whether he has had a similar experience.

The patient on whom I made this observation presented no symptoms of pregnancy. Her only symptom was a slight upper abdominal discomfort which I regarded as due to some gastric disturbance. While in the radiologic laboratory, this patient suddenly collapsed and was sent to the hospital where her blood pressure was 58 systolic and 39 diastolic. The blood count showed 4,000,000 red cells, 69 per cent

hemoglobin and 48,000 leucocytes. A second count later showed 2,925,000 red cells, 35 per cent hemoglobin and 35,000 leucocytes. A third count showed much the same figures. Vaginal examination disclosed only a slight tenderness on pressure on the right side, and as the cervix was moved upward there was pain. Dr. Musser, Professor of Medicine at Tulane University, expressed the opinion that she had a hemorrhage and stated that acute hemorrhage in the abdominal cavity would give a high leucocyte count. We operated upon her and found an opening about the size of my right thumb into the horn of the right tube. She is now doing quite well.

DR. DAVID A. HORNER, CHICAGO, ILL.—An important point to consider is, when does an ectopic pregnancy become an abdominal pregnancy. Occasionally there are good reasons for not operating at once, especially if it has been some time between the apparent rupture and admission to the hospital. I have at the present time two ectopic pregnancy babies going to school, simply because the mothers were not operated upon at the time the rupture of the pregnancy occurred.

Chronic ectopic pregnancy (I think I can call it that) is seen more often in charity hospitals than in private practice. The chronic case is the acute one which was unoperated upon and which went on to recovery, the acute symptoms subsiding when the extruded mass developed to term or was totally absorbed.

The point I wish to bring out is that it is not necessary to operate upon all ectopics immediately on diagnosis. Stilbestrol will stop functional uterine bleeding but will not stop a case of uterine bleeding following a ruptured ectopic pregnancy. Hence this point may help in the diagnosis of some cases of ruptured ectopic pregnancy.

DR. KARL JOHN KARNAKY, HOUSTON, TEXAS.—I am at the present time studying the cases of ectopic pregnancy at the Jefferson Davis Hospital, Houston, Texas. In the cases from 1932 to 1933, which have so far been reviewed, there were 11 white women, 5 Mexicans, and 16 colored women, a total of 32 cases. The ages were from 17 to 49, the majority of cases were at the age of 24 years.

The preoperative diagnoses were as follows: ectopic, 11; infected abortion, 2; acute salpingitis, 3; pelvic tumors, 2; tuboovarian abscess, 5; and acute abdomen, 3.

One point of interest was brought out by 6 cases of ectopic pregnancy referred to the Menstrual Disorder Clinic of the Jefferson Davis Hospital because of vaginal bleeding. When we gave these women stilbestrol to control their uterine bleeding, they did not stop bleeding.

DR. E. F. SCHNEIDERS, MADISON, WIS.—There are two procedures that have been of great value in the treatment of patients in extremis after trips to the hospital from rather distant points. One is the use of autotransfusion. I have resorted to autotransfusions in a number of practically moribund patients with success. In many of these cases we have dipped the blood by means of a sterile glass into a beaker, filtered it through triple gauze into citrate solution and have then transfused these patients with their own blood.

The other point was the use of large transfusions. Some patients have been in so much shock and have lost so much blood that the ordinary amounts are not adequate. In such patients we have used up to 1,500 or 1,800 c.c. of blood. We have cross-matched donor to donor to avoid possible allergic reactions and have tried not to use donors who have had a recent meal. The blood banks and the use of plasma may obviate the necessity of either autotransfusions or massive transfusions, but in the past these two measures have been of distinct help in our practice, and I believe are worthy of use when immediate donor or blood bank is not available.

DR. E. W. FISCHMANN, CHICAGO, ILL.—I wish to defend the exploratory colpotomy in preference to diagnostic cul-de-sac puncture. In a great many cases by exploratory colpotomy we have been able to inspect both tubes and in some have been able to remove the tube containing the ectopic pregnancy. Often this can be done very nicely under local anesthesia. In some cases, on the other hand, we have found it easier to cut the vesicouterine pouch than the rectouterine pouch. We firmly believe that the vaginal route is one that should be practiced more often than the abdominal route, particularly where the diagnosis is not certain.

Another point I might emphasize in the operative treatment of ectopic pregnancy is that the simultaneous removal of the appendix in these cases adds to the hazard of the operation. We have found in a study of our cases at the Cook County Hospital that simultaneous removal of the appendix in cases of ectopic pregnancy definitely increases the morbidity and mortality in these cases.

DR. JOHNSON (closing).—We have classified our cases into three groups, as they were admitted to the hospital, and attempted to show that although they are all ruptured ectopic pregnancies, they require three different types of surgery. The majority of the operative work was done by the resident staff. We do not advocate removal of appendices in any case with blood in the peritoneal cavity.

In the more acute group, 60 per cent of cases had transfusions, with only unilateral salpingectomies being performed. In the second group, only 31 per cent had transfusions, with indicated surgery carried out. The patients in the third group were admitted, in most instances, as cases of pelvic inflammatory disease. Only 16 per cent of these had a correct diagnosis before operation, yet they were ruptured ectopic pregnancies from two to six months after the rupture. In these cases we advocate correction of the pathology presented.

We emphatically believe in immediate operation on the acute cases of ectopic pregnancy, and the more radical work was carried out only in cases of long standing, and in those patients over 35 years of age. We do not advocate radical surgery on young women.

In reference to Dr. Phillip's case, we had a few cases with leucocytosis of from 25,000 to 30,000 white blood cells. I do not present this as a diagnostic point, but the cases with the highest counts were usually those with cornual ruptures, or massive hemorrhage. In those cases we see the most profound shock.

Dr. Horner advocates conservatism on abdominal pregnancies. All of the fetuses in the abdominal pregnancies in our series were dead at time of operation, and we considered these as tubal abortions. We do not, however, practice conservatism with ruptured ectopic pregnancies or abdominal pregnancies, for the maternal mortality will be higher, and, considering the deformities associated with abdominal pregnancies, we prefer to save the mother rather than have a deformed child.

Dr. Fischmann's exploratory colpotomy in skilled hands may be satisfactory, but I do not care to have my hands tied by removing a ruptured ectopic pregnancy per vaginam, and then have an ascending infection follow. The first principle of good surgery is to have proper exposure. Vaginal exploratory colpotomy does not lend itself readily to adequate exposure with ectopic pregnancy. Diagnostic puncture of posterior cul-de-sac is of diagnostic importance.

Dr. Schneiders is right in advocating large transfusions. We gave transfusions in 60 per cent of the first group, and anywhere from 1,500 to 2,000 c.c. of blood or plasma were used. Massive transfusions are excellent when indicated, and we should never overlook the use of the patient's own blood when found in the peritoneal cavity.

CLINICAL APPLICATION OF ERGONOVINE DURING THE THIRD STAGE OF LABOR*

A. W. Diddle, M.D., Iowa City, Iowa

(From the Department of Obstetrics and Gynecology, State University of Iowa)

Ergot was first introduced into obstetric practice by Stearns as "pulvis parturiens," but a few years' experience with administration during labor, according to his recommendation, proved that it was too powerful and dangerous for that purpose. It soon became an established conviction that this drug should not be exhibited until the uterus was empty, and today it is commonly considered that oxytocic drugs, especially ergot, cannot safely be given until after expulsion of the placenta.

Isolation of the water-soluble, oxytocic principle, ergonovine, has provided the profession with a dependable ergot preparation suitable for intravenous use, and has stimulated search for further clinical applications. More recently, certain clinics have reported that ergonovine given intravenously just before completion of the second stage hastens separation of the placenta, reduces the average blood loss, and diminishes the incidence of post-partum hemorrhage. The procedure is, however, still controversial.

Prior to April 1, 1940, oxytocics had rarely been given at the University of Iowa until after expulsion of the placenta. The exceptions included the occasional instances of third-stage hemorrhage from incomplete placental detachment or unusual prolongation of this stage of labor. No attempt was made to deliver the placenta until there were evidences of separation or the appearances of unusual bleeding. Beginning April 1, 1940, ergotrate (grain $\frac{1}{320}$) in solution was routinely injected intravenously into an antecubital vein with delivery of the anterior shoulder in vertex presentations and at the time of extraction of the head in breech. At the first ensuing contraction, the uterine fundus was grasped by the Credé grip and strong pressure was exerted to expel the placenta, which was usually born within three minutes of the birth of the child.

This study concerns the evidence obtained in 1,960 consecutive deliveries between April 1, 1940, and March 31, 1941, when intravenous ergonovine was used routinely in the great majority of patients, as compared with the results in the preceding twelve-month period, when oxytocics were ordinarily not given until after expulsion of the placenta.

*Presented at the Thirteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, New Orleans, La., October 2 to 4, 1941.

The material in the two series was reasonably similar. Sixty-five per cent of the women in each series were parous. Ante-partum bleeding due to placenta previa or abruptio placentae occurred in nine of the ergonovine group and in five of the controls. The birth weights were comparable, as was the incidence of multiple pregnancy and other factors predisposing to uterine atony.

PROCEDURE

Post-partum hemorrhage has been defined, in accordance with common practice, as the loss of 600 or more cubic centimeters of blood.

A sterile basin held against the perineum during the period of active bleeding was employed for collection of blood. Additional and uncollected blood was "estimated" and added to make the total loss. It is recognized that values obtained in this fashion are subject to criticism, but it is believed that the method at least indicated abnormal blood loss with reasonable accuracy. For the purpose of this study, and in view of the method of collection, patients who lost between 500 and 600 c.c. of blood are included.

RESULTS

Incidence of Hemorrhage.—The actual incidence of bleeding in excess of 500 c.c. is shown in Table I. It is evident that the loss of more than

TABLE I. INCIDENCE OF POST-PARTUM HEMORRHAGE

YEAR	TOTAL DELIVERIES	PATIENT WITH POSTPARTUM HEMORRHAGE		REMARKS
		NUMBER	PER CENT	
Pre-ergonovine group; 4-1-39 to 3-31-40	1761	181	10.3	Oxytocic usually not given until after delivery of the placenta
Ergonovine group; 4-1-40 to 3-31-41	1960	78	4.0	Ergonovine given before delivery of the placenta

500 c.c. of blood was diminished considerably by the injection of ergonovine early in the third stage.

Figures for the two series were then grouped according to the total blood loss (Table II). It is now evident that the use of ergonovine

TABLE II. THE INCIDENCE OF POST-PARTUM HEMORRHAGE AT VARIOUS LEVELS

BLOOD LOSS IN CUBIC CENTIMETERS	CONTROL SERIES (1,761)		ERGONOVINE SERIES (1,960)	
	NO.	%	NO.	%
500- 600 (minimal hemorrhage)	100	5.6	37	1.8
601- 800	42	2.5	18	0.9
801-1,000 (excessive hemorrhage)	17	1.0	11	0.56
1,001-1,499	19	1.1	9	0.45
1,500 and over	3	0.17	3	0.15
Total (over 600)	81	4.6	41	2.1
Total (over 500)	181	10.3	78	4.0

reduced the blood loss in the 500 to 600 c.c. group, as well as in the cases of post-partum hemorrhage as defined earlier. Blood losses of more than 600 c.c. occurred in 81 (4.6 per cent) of the 1,761 control cases, as against 41 (2.1 per cent) of the 1,960 given intravenous ergonovine. Except in the small groups which suffered excessive blood losses (over 1500 c.c.), the ratio between the two series approximated 2:1.

"Retained placenta" was diagnosed when the third stage was protracted two hours or longer, while "partially detached placenta" included those cases in which unusual bleeding before delivery of the organ demanded intervention. By these definitions there were 4 retained placentas, 3 in the ergonovine and 1 in the control series. The blood loss ranged from 700 to 1,450 c.c. Manual removal of the placenta was performed three times (2 ergonovine and 1 control) after liquid distention of the umbilical cord and placenta and Credé maneuver under anesthesia had proved unsuccessful. In the fourth instance, Credé expression was successful.

Partially detached placentas were encountered in 10 patients (6 ergonovine and 4 control). The blood loss varied from 800 to 2,000 c.c. In 2 of the control series, distention of the cord and placenta made Credé expression of the organ possible, while in the remaining 8, manual removal was necessary.

In 2 undiagnosed twin pregnancies, ergonovine was given just before birth of the first child, but delivery of the second fetus offered no complication. In cases of multiple pregnancy generally, the loss of more than 500 c.c. of blood was reduced from 1:3 to 1:17 by the injection of ergonovine.

On the other hand, there was no appreciable reduction in the incidence of high blood loss in women giving birth to children weighing more than 4,000 Gm. In both groups, approximately 10 per cent of these mothers lost more than 500 c.c. of blood.

Operative delivery generally increased the blood loss and the indicated use of ergonovine did not effect this cause of post-partum hemorrhage. In the control year, 20 per cent of the hemorrhages occurred in operative cases, while in the following twelve months the incidence was 28 per cent. During the two one-year periods, the operative incidence was between 12 and 15 per cent. In at least one-third of the hemorrhages associated with operative intervention, cervical or perineal lacerations explain the excessive blood loss, whereas in the remainder, uterine atony, possibly incident to deeper and more prolonged anesthesia appeared to be of etiologic significance.

Excessive bleeding attributed to uterine atony occurred only once in 217 cases (0.46 per cent) among the ergonovine series, as against one in 55 (1.8 per cent) among the controls. As usual, over-distention of the uterus by twins, hydramnios, and large babies predisposed to inertia.

Prolongation of labor (thirty hours or more) produced no appreciable effect, whereas precipitate labors (less than three hours) predisposed to excessive bleeding. The use of ergonovine seemed to reduce bleeding from this cause, since there were less than one-half as many blood losses of 500 or more cubic centimeters in the ergonovine than in the control group. Presumably the oxytocic acts by preventing the lag of uterine contractions after its tumultous first- and second-stage activity.

The intrapartum use of posterior pituitary extract is said to increase the incidence of post-partum hemorrhage (Reich, 1939). This oxytocic was not employed during labor in either series here reported, but was administered to approximately one-half the individuals in both groups as a part of the induction of labor. There was no evidence that such use influenced the post-partum blood loss.

Puerperal Morbidity.—The diagnosis of febrile puerperium is made whenever the temperature rises to 100.4° F. or more on any of the first ten days after delivery. Temperatures are recorded six times daily at four-hour intervals. Among the patients of the ergonovine series such febrile reactions occurred in 34.8 per cent, while in the control group the incidence was 38.6 per cent. This difference (3.8 per cent) is not significant, particularly since more attention was given to the replacement of lost blood during the year when ergonovine was employed as a routine.

Maternal Deaths.—There were 3 maternal deaths associated with excessive bleeding in the series treated with ergonovine, but none among the controls (Table III). Each death was associated with unusual blood loss, but, except in one instance, there was no reasonable basis for implicating the administration of ergonovine. One patient had placenta previa with post-partum uterine atony and died from shock; another had eclampsia and developed severe shock with hemorrhage after delivery. In both instances, transfusions were ineffective although given promptly from the blood bank. The third death followed a poorly managed premature and prolonged labor. The placenta did not detach completely and was retained behind a constriction ring, together with a considerable quantity of clotted blood. Attempts to complete separation by inflation of the placenta and by the Credé maneuver were unsuccessful, and manual removal was done four hours after birth of the baby. In spite of intravenous fluids, blood transfusions, and other usual antishock measures, death occurred an hour later.

DISCUSSION

The ultimate fate of any new clinical procedure depends upon two factors: it must not lead to any harmful reactions, and it must be better than its therapeutic predecessor. All treatments are eventually judged by such standards. When a procedure is designed to replace

TABLE III. MATERNAL DEATHS

CASE	PARITY	AGE	PRESENTATION	TRANSFUSION IN C.C.	DURATION OF LABOR	DURATION OF THIRD STAGE	METHOD OF DELIVERY	BLOOD LOSS IN C.C.	WEIGHT OF BABY IN GRAMS	REMARKS
40-10112	vi	29	R.O.A.	1500	2 hr., 42 min.	2 min.	Version and extraction	2,000	3,850 (stillborn)	Placenta previa; postpartum uterine atony; no anesthesia. Died 10 minutes after delivery.
41-1867	0	20	R.S.A.	350	10 hr., 23 min.	9 min.	Breech extraction	750	2,800 (stillborn)	Eclampsia; shock; uterine atony post partum; no anesthesia; died 13 hours after delivery.
41-1559	iii	25	R.O.A.	500	30 hr., 38 min.	4 hr.	Spontaneous	1,300	2,230 (alive)	Hypertensive cardiovascular disease; Partially detached placenta; shock; nitrous oxide anesthesia; died one hour after delivery.

therapy which has behind it a long and honored tradition, it must be viewed very critically.

There is good evidence to indicate that during the normal third stage placental detachment occurs with the first uterine contraction. Expulsion of the afterbirth into the lower segment or vagina is a function of succeeding contractions, and spontaneous expulsion from the vagina may take some hours. Because of the slowness of this last part of the phenomenon, it has long been considered good practice to expel the placenta by uterine pressure as soon as there are signs that it has been extruded from the uterine cavity.

The present experimental procedure is designed to hasten the earlier phases of the mechanism of placental expulsion by increasing the strength and amplitude of the initial third-contraction which detaches the organ. Prompt expulsion is then prompted by uterine pressure.

The mere fact that the new technique materially shortens the third stage should not be given serious consideration, since speed at this time is of no consequence. If, however, it can be shown that the blood loss is reduced, the number of post-partum hemorrhages diminished, and that serious complications of the third stage are not increased, then the procedure must receive serious consideration. Except in institutions with plenty of personnel, the plan will not prove practicable, because it demands an additional assistant to give the injection at exactly the proper time and to follow through with properly directed uterine pressure.

The data presented indicate that, when properly carried out, the intravenous injection of a therapeutic dose of ergonovine just preceding expulsion of the shoulders (in vertex presentations) or of the after-coming head (in breech presentations) is practically devoid of serious consequences and is effective in reducing the incidence of post-partum hemorrhage due to uterine atony. This experience confirms that of other observers (Reich, 1939; Eastman, 1939; Davis, 1940). It was, however, noted that more than 50 per cent of post-partum hemorrhages occurred within five minutes of expulsion of the child as against 15 per cent in the control group. This change may be attributed to the early vigorous uterine pressure required by the technique. The evident increase in the number of retained placentas (3 as against 1 in the controls) with the greater number of hemorrhages from partial separation of the placenta in the same group (6 to 4) makes the combined incidence of these more serious anomalies of placental separation and expulsion, 9 in the group receiving ergonovine and 5 in the control group. It appears that this type of intervention increases these major difficulties. This would, of course, constitute a very valid argument against the new practice, since a large part of the third-stage hazard revolves around these complications. It should, however, be recognized that this use of

ergonovine requires accurate timing to attain its maximal value and that experience is necessary to ascertain the proper time for the injections.

Sufficient time has not yet elapsed and accumulated experience is not yet large enough to permit accurate evaluation of the procedure. Consequently, it seems reasonable for the clinics interested to continue their experiments until the combined data become statistically significant. At present it is probably preferable that institutions with a minimal number of birth-room assistants refrain from employing this type of interference with the normal mechanism of the third stage. By and large, attempts to improve upon nature are not eminently successful.

CONCLUSIONS

The intravenous injection of ergonovine shortly before the conclusion of the second stage of labor appears (1) to shorten the placental stage, (2) to diminish the average blood loss, (3) to reduce by one-half the number of patients who suffer post-partum hemorrhages, but (4) to almost double the incidence of the more serious anomalies of the third stage, retained placenta and partially detached placenta.

This technique should still be viewed as experimental and should not be adopted generally until sufficient evidence has been accumulated to permit a reliable statistical evaluation of its associated dangers.

Ergot is manufactured as "ergotrate" by Eli Lilly and Company.

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DISCUSSION

DR. HARRY A. PEARSE, DETROIT, MICH.—Dr. Diddle has used 500 to 600 c.c. of blood loss as his criterion for diagnosing post-partum hemorrhage. Since women vary considerably as to how much blood loss they will tolerate, Pastore and others state that it should be expressed in terms of body weight, 1 per cent or more loss being indicative of post-partum hemorrhage. I would like to emphasize the value of actual measurement. Those who have not done this will be amazed at the difference a forceps operation or an episiotomy makes in the blood loss. In that regard the low operative interference in this series is very commendable.

Our experience with ergonovine at The Florence Crittenton Hospital in Detroit is essentially the same as the essayist's. We have been using neogynergin which is ergotamine tartrate plus ergobasin, ergonovine being the name chosen by the American Medical Association for the water soluble oxytocic principle in ergotrate, ergometrin, ergobasin, and others.

The first method used by us called for the administration of 1 c.c. of ergonovine immediately following the birth of the baby. This was given in two ways, first intravenous, and then intramuscular. It was found in these cases that a contraction of the uterus would occur, clamping down upon the placenta and reducing the amount of blood lost in the third stage. Given at this time it was found that

frequently only a portion of the placenta would be sheared off by the action of the ergonovine and bleeding would continue until the one area which remained attached was completely separated. Some of these cases took as high as twenty-eight minutes to separate, with a considerable loss of blood. As a result, the average time for the entire series was a third stage of fourteen minutes and a blood loss of 400 to 500 c.c.

A different technique was then adopted in which 1 c.c. of ergonovine was given to the mother intravenously as soon as the anterior shoulder of the baby presented itself. Following the birth of the baby, the uterus was followed down and the placenta extruded as soon as possible. The adoption of this technique was followed by a drastic reduction in the time and the amount of blood lost in the third stage, compared with the previous method. In the second method, the mechanism of the third stage was changed so that instead of the placenta being separated by the formation of a retroplacental clot, it was separated by a shearing motion caused by the violent contraction of the uterus following the injection of the oxytocic drug. The average time of separation in this series was two and one-half minutes, the average loss of blood 125 c.c.

There were no actual retained placentas found in this group, but some placentas which had been separated and thrown down into the lower uterine segments were retained in that site and removed by extraction. Although we did not have any retained placentas in our series, the possibility of this occurring is still great. Another possibility that we must think of which at the present time has not been investigated is the possibility of a cotyledon of the placenta being separated and retained during the shearing process. The force of this shearing process was experienced in a manual removal of a portion of retained placenta when the injection was given and the hand withdrawn as the uterus began to contract down. The statement that shortening the third stage does not deserve serious consideration might be argued if we couple with it the fact that the longer the third stage, the greater the blood loss.

The author's conclusion is wise: that this procedure is not available for general adoption and I agree that, by and large, attempts to improve upon nature are not eminently successful.

DR. JAMES R. MANLEY, DULUTH, MINN.—Last year we ran a small series of 50 cases, using ergotrate intravenously and compared them with 50 cases in which ergotrate was given into the muscle after the placenta was expelled. We, too, found that with the former procedure there was a marked reduction in the amount of blood lost. We gave the ergotrate as soon as the anterior shoulder was born and we expressed the placenta within two or three minutes. We had no bad results, except one retained placenta.

We came to the same conclusions as the essayist, namely that it is not a procedure to be used in a general hospital, where oftentimes the intern is busy helping the obstetrician in a delivery by forceps and cannot be responsible for the giving of the ergotrate. Intravenous ergotrate is very valuable in post-partum hemorrhage and in cesarean section.

DR. R. E. ARNELL, NEW ORLEANS, LA.—During the past three years we have been investigating the effects of various oxytocic drugs on the third stage of labor. Blood losses were determined by an exact chemical-colorimetric method whereby the amount of hemoglobin loss (in grams) in free blood, clots, sponges and drapes, is converted into cubic centimeters of blood. This is a more exact method of determining blood loss than either clinical estimation, which is usually grossly inaccurate, or volumetric measurement (Pastore) of all fluid lost, which may include amniotic fluid and urine as well as blood.

The chart reveals our results in 500 consecutive normal cases (Table I).

TABLE I. EFFECTS OF OXYTOCIC THERAPY ON THE THIRD STAGE OF LABOR

	CASES	AVERAGES		COMPLICATIONS
		BLOOD LOSS IN C.C.	DURATION IN MINUTES	
No oxytocic	100	182	8.4	2 post-partum hemorrhage (over 500 c.c.) 3 excessive bleeding (300 to 500 c.c.)
Ergotrate intravenously with anterior shoulder	100	48	2.1	1 retained detached placenta (shoe-horn removal)
Ergotrate intravenously 1 min. after delivery of the baby	100	145	6.2	1 excessive bleeding (300 to 500 c.c.)
Pituitrin intramuscularly with anterior shoulder	100	106	4.5	None
Pitocin intramuscularly with anterior shoulder	100	78	4.4	None
Totals	500	111	5.1	

An evaluation of the results of intravenous administration of ergonovine with the delivery of the anterior shoulder of the baby may be summarized as follows:

Advantages.—

1. Diminishes blood loss during and after the third stage.
2. Lowers incidence of post-partum hemorrhage and the necessity for packing the uterus. The incidence of uterine tamponade on our service is now only one in 640 deliveries.
3. Shortens length of third stage, duration of anesthesia, etc.
4. Lowers incidence of infection.
5. Eliminates danger of individual susceptibility and anaphylaxis and can be used in the toxemias of pregnancy.

Disadvantages.—

1. Administration requires an assistant.
2. Good timing is necessary so that separated placenta can be expressed immediately.
3. Infrequent possibility of hour-glass contractions of uterus or spastic cervix requiring manual removal of placenta.
4. Danger of administering in case of undiagnosed twins.

DR. DIDDLE (closing).—Your personnel should be trained to the use of this drug. Every time we change interns the incidence of retained placenta increases. In the last six weeks we have had three out of 225 cases. When the intern becomes accustomed to its application, the incidence drops.

The use of ergonovine is to be continued indefinitely by us until a larger number of cases is collected to give more definite conclusions. Even though the drug may be recommended in large clinics it probably should not be made available in smaller institutions that have a limited personnel.

EFFECT OF LYMPHOGRANULOMA VENEREUM ON PREGNANCY, LABOR, AND THE FETUS*

C. LEON WILSON, M.D., AND H. CLOSE HESSELTINE, M.D., CHICAGO, ILL.
(From the Departments of Obstetrics and Gynecology, Provident Hospital, The University of Chicago, and the Chicago Lying-in Hospital)

WHENEVER an infectious process occurs in a gravid patient, an understanding of the effect of the disease upon the product of conception and parturition, of the alteration of the course of the disease because of the pregnant state, and of the possibility of transmission to the fetus and newborn is apropos.

Lymphogranuloma venereum is rare in private patients, but more common in the charity services, especially among the colored race. The concomitant presence of lymphogranuloma venereum and pregnancy is striking because of its infrequency. Perhaps a few cases with minimal or no residual change remain undiagnosed. Within the past four and one-half years (Dec. 24, 1936, to June 30, 1941), 17 such patients have been observed at the Provident Hospital, whereas within the past ten years (May 25, 1931, to June 30, 1941) only one such patient has been diagnosed at the Chicago Lying-in Hospital. This rarity along with the infrequency of other pelvic neoplasms emphasizes the need for evaluation of the pelvis on prenatal examination, particularly in view of a few isolated reports which stress the possibility of tragedy at delivery both to the mother and the newborn. Nevertheless, the observations listed below do not agree with some references that termination before viability or in stillbirth is problematic merely because of this venereal disease damage. Perhaps during the active infection such hazards confront the fetus. More likely a relative sterility persists either because of pathologic alteration from an extensive inflammatory process of the disease or perhaps from other disease processes. It is not the rectal stricture as such that produces dystocia, but the associated perirectal hyperplastic or inflammatory reaction which obstructs the passage. The parturient uterus probably functions normally.

Repeated examinations before conception, during pregnancy, and after delivery have shown no noticeable alteration in the course of the disease or a change in the inflammatory tissue mass as a result of the pregnancy. All in this series were in the chronic or latent stages. Not one patient came to the prenatal clinic in the active state or developed an active process while under prenatal care. Possibly such stages did exist, but in any event the active stage went unnoticed.

*Presented at the Thirteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, New Orleans, La., Oct. 2 to 4, 1941.

Whether the secondary state (systemic manifestation) of lymphogranuloma venereum would be associated with a different effect upon the fetus cannot be stated from our study or from the publications. Certain agreement may be found between this group and some reports that there is an increased abortion, premature labor, and stillbirth rate among women with this venereal disease. Even so exception must be taken because the data are from the histories prior to the pregnancies in question. As a matter of fact, the number that carried to term were well within the normally expected range. This may be challenged; first, for these prospective mothers may no longer harbor the virus and thus are free from the infection; second because early unintentional abortions may have occurred in many who did not seek obstetric care.

LITERATURE

Ample and adequate reviews on etiology, pathology, symptomology, diagnosis, treatment, and prognosis of lymphogranuloma venereum have come from the pens of Frei;[15] D'Aunoy and von Haam;[10] Torpin, Greenblatt, Pund and Sanderson;[31] Kamouchi;[20] Buendia;[8] Shropshear;[28] Stein;[30] Knight and David;[21] Barber and Murphy;[5] Coutts;[9] and many others. Should the infections remain localized not much chance would exist for fetal involvement: but recently convincing evidence has been given which proves the possibility of systemic infection. Von Haam and D'Aunoy[33] reported the presence of the virus in the spinal fluid, but they were unable to indicate the incidence in which central nervous system infection may be expected. Gutman[18] amplifies this point to the extent that systemic manifestations occur with sufficient frequency to be of general medical interest.

The present methods of demonstration of the virus in the blood stream of human beings serve inadequately, but Benedek and Olkon[7] have confidence in the ultimate completion of this link. The systemic involvement and multiplicity of lesions are vouched for by Jones and Rome,[19] Becker,[6] Baneiu and Caratzali,[4] and Kornblith.[22]

The skin, bones and joints, eyes, throat, central nervous system, and other structures serve as a nidus and may become extensively injured. Thus the product of conception (the fetus and the placenta) must rely upon its own defense mechanism for its self-protection when its mother has a systemic involvement.

If the fetus acquires the infection it would surely show clinical evidence or give, after its birth, a positive reaction to the Frei antigen since in the adult the reaction is long standing if not permanent. Dick[11] emphasizes that the problem of transmission is unsettled although he reported one case with a positive reaction in an infant aged 2 weeks and again five months after birth. This last test gave a lesser response but with a weaker antigen. This reaction may result from passive transmission. Dick tested ten normal newborn infants to find negative reactions. Durel's[13] investigation on 32 infants without clinical evidence of lymphogranuloma venereum produced all negative reactions. When compared to the 100 infants of Babonneix[3] with only 3 transiently positive tests, much doubt may be cast upon the frequent likelihood of false positive tests and some assurance given to the contention of passive transmission of antigen reaction "bodies." More pointedly, Sonck[29]

examined 19 children born of mothers who during pregnancy or parturition suffered with a process of lymphogranuloma venereum (termed active, but more likely residual or latent). The first 12 tested by antigens gave definite negative reaction. Two others had only detailed physical examinations, while the remaining 5 were examined, but not tested, by others.

The indisputable evidence of Dummer and Tamura,[12] Melczer and Sipos,[25] Sonck,[29] and Levy[23, 24] established the juvenile or premenacmic* group and at the same time emphasizes that these are not congenital transmission but acquired infections after the natal day. These children developed the same types of syndrome as the adult.

The rarity of pregnancy occurring in a patient with lymphogranuloma venereum lacks complete explanation. Schutte and Lubitz[27] had no pregnancies in 17 patients with this disease. Gray and Barnes[17] discovered 3 positive tests in 59 colored and no positive tests in 68 white prenatal patients. At the Provident Hospital, the incidence in pregnancy is approximately 0.5 per cent or roughly one in 200 out of 3,500 pregnancies, while in contrast at the Chicago Lying-in Hospital only one has been discovered in 27,000. Gray and Barnes raised the question whether there is some degree of sterility from the disease per se or whether these patients are sterile from other causes.

Not one reference is made to show that the maternal course of pregnancy was altered in the slightest. The wise and timely reports reveal that both maternal and fetal lives were lost because of the complication of pelvic obstruction at the time of delivery. Gaines and McDowell[16] recommend abdominal delivery when sufficient obstruction prevails as one patient died after a rupture of the rectum into the peritoneal cavity from association with version and extraction after "failed forceps." R. E. Anderson[2] lost a patient because of a ruptured uterus in association with version and extraction in an attempt to deliver the fetus. Vignes[32] states that not one of 12 women was able to bear a living child, as all attempts ended in stillbirth or neonatal death. An unexpectedly short labor in H. E. Anderson's[1] case in spite of the rectal stricture and perirectal mass eclipses the illumination of the foregoing. Even a single instance as Fagarasano's[14] proves the possible danger of intestinal obstruction by rectal stricture during pregnancy. Michelson, Crotty and Kasselberg[26] stress that mothers with external lesions may give birth to babies physically normal and persistently test negative.

DATA AND COMMENT

Comparable to all clinical data many factors play their part in the summation. Not one maternal mortality occurred in these unselected 18 women. The syndrome of lymphogranuloma venereum as a complication of pregnancy was not recognized prior to 1936 at the Provident Hospital. The diagnosis was made by the presence of the syndrome and a positive Frei test.

The first abortion in the group was unintentional. The colostomy presumably had no bearing upon the interruption of the gravid state and presumably the disease was not the cause.

*Menacme is defined by Dorland as "that period of a woman's life which is marked by menstrual activity." Premenacmic would be the adjective denoting the period prior to the menacme. (H. C. H.)

The second abortion and the first therapeutic one was done because of a severe anemia and generally very poor condition. Post-partum sterilization protected against a repetition.

The third gravid patient in which this complication occurred had had a complete obstruction of the bowel relieved by a colostomy before conception in which this complication occurred. The pelvic cavity was decreased slightly by the tissue reaction. Because of the possible need for abdominal delivery in the presence of a colostomy opening, the pregnancy was terminated, but sterilization was deferred in the hope that enough improvement would take place in the rectum to permit closure of the colostomy. If then a pregnancy occurred and abdominal delivery became necessary, it could be done with greater safety theoretically. The next pregnancy occurred about one year later but the patient postponed coming to the prenatal clinic until the last trimester. The pregnancy proceeded normally to term without symptoms even with the bowel fixed at the colostomy opening and during the ensuing labor. The inflammatory tissue yielded sufficiently for normal vaginal delivery.

The two patients with colostomies (carrying their pregnancies to term) had a normal parturition and convalescence. Twice cesarean section was employed to accomplish the delivery, both times because of frank obstruction by "soft" tissue masses. The most severe one (4) had fixed pelvic mass above an extensively necrotic vaginal wall and had externally a pronounced elephantiasis of the vulva. The second patient (5) presented the mechanical blocking without the destructive process.

In Case 7, an extensive fecal impaction above the rectal stricture prevented the presenting part from entering the true pelvis. By means of dilatation of the rectal stricture and repeated enemas the fecal mass was removed after which normal descent and delivery of twins took place. The only forceps delivery was in the white patient at the Chicago Lying-in Hospital (1940). This low forceps operation was indicated for other conditions than those resulting from the process of the lymphogranuloma venereum.

These 18 mothers (17 colored and 1 white) received obstetric care in 21 gestations during this study. Two therapeutic and one unintentional abortions account for the 3 losses of fetal life. Two mothers each had repeat pregnancies going to term uneventfully under these observations, while one had twins.

These same 18 mothers had 58 pregnancies in all, 21 of which came under this study directly. There were 37 prior to the first visit. From this number, abortions, stillbirths, and neonatal deaths, a total of 11, reduced the number of living fetuses to 27. One of the four abortions was induced. The 6 stillbirths and neonatal deaths are without explanation. The abortion rate is within the expected range but the loss of life, because of prematurity or other causes, is abnormally high. This finding agrees in part with certain contentions that one should anticipate this in these cases, but lacking specific information such a deduction is not justified.

The gestations under study carried to or near term and culminated in 19 living births (no stillbirths or neonatal deaths). All 19 babies were tested intradermally with at least one or more known dependable antigens from human sources. Twelve newborn infants were tested with mouse brain antigen and mouse brain control as well as with

TABLE I

PATIENT	AGE	PREGNANCY PRIOR TO GESTATION IN QUESTION				LESION AND OTHER COMPLICATIONS	DELIVERY	BABY
		*TOT.	LIV.	S & N	ABORT.			
Abortion—Therapeutic and Unintentional								
1	35	1	1			Rectal stricture; Colostomy	Abortion unintentional	
2	28	3	3			Rectal stricture; anemia, poor condition	Therapeutic abortion; sterilization	
3	31	1			1	Rectal stricture; fistula; Colostomy	Therapeutic abortion	
Normal and Operative Deliveries								
4	23	4	3		1	Rectal stricture; vaginal slough; syphilis	Cesarean section	Normal
5	26	2	1	1		Rectal stricture; pelvic mass	Cesarean section	Normal
6(W)	40	1	1			Rectal stricture; fistula; heart disease	Low forceps	Normal
7	32	1	1			Rectal stricture; fecal impaction	Normal—twins	Normal
3	33	+1			+1	Rectal stricture; fistula; colostomy	Normal	Normal
8	23	0				Elephantiasis; vulval and vaginal ulceration	Normal	Normal
8	25	+1	+1			Vaginal scarring	Normal	Normal
9	33	4	3	1		Rectal stricture; fistula	Normal	Normal‡
9	34	+1	+1			Rectal stricture; fistula	Normal	Normal
10	26	4	3	1		Rectal stricture; condyloma; syphilis	Normal	Normal
11	26	3		3		Rectal stricture	Normal	Normal
12	24	0				Rectal stricture; elephantiasis	Normal	Normal
13	30	4	3		1	Rectal stricture; colostomy	Normal	Normal
14	30	0				Rectal stricture; fistula	Normal	Normal
15	32	1	2 (twins)			Rectal stricture	Normal	Normal
16	32	2	1		1†	Rectal stricture	Normal	Normal
17	37	1	1			Rectal stricture	Normal	Normal
18		2	2			Rectal stricture	Normal	Normal
Total		37	27	6	5	18 patients: 21 pregnancies; 22 fetuses 19 term; 3 abortions		

*Tot., total; liv., living; S & N, stillbirths and neonatal deaths; abort., abortion; W., white; +, add one more to total first listed for given patient.

†Induced abortion.

‡Baby gave positive Frei reaction on third and tenth days only.

human test materials. These were made within the first ten days of life on 13 babies born from 10 mothers (2 repeat pregnancies and one twin pregnancy). Only one baby out of 13 gave a positive test and these readings were made on the third and tenth days. Even this infant had a negative test within three months, and it has since remained negative. All babies were completely or partially breast fed by their mothers. Therefore breast feeding was apparently safe in these 19 instances.

All 19 are clinically free from the disease and appear physically and mentally normal.

It is pointed out that all of these mothers were apparently in the latent stage of the disease, and therefore probably noninfectious. If this is correct, and it appears that it is, then the hazards to reproduction involve first the consideration of whether the residual damage produces a sterility. No evidence is at hand on this point. Although skin tests have not been made, clinical evidence points out that sterility is not a part of the picture. Next, if conception occurs what may happen to the product of it. Thus far it seems safe to predict that it is safe for the fetus during latency. The mothers were not made worse nor was the process obviously altered. Labor began at or near the end of pregnancy (within normal range limits) and pursued its usual course successfully unless the birth canal was insufficient.

Only 7 placentas were examined microscopically. The histologic pattern was normal in all which is in accord with the gross appearance of the entire series.

It would be worth while indeed to find a sufficient number of pregnant women who had the disease in the active phase, particularly if one could prove a systemic manifestation in them. If this virus passed through the placenta, much damage could result, but again the fetus, like its mother might have little or no residual damage. If, on the other hand, the damage was severe, extensive or lethal, an abortion or stillbirth could be expected.

All pregnancies continued without special therapy for the venereal disease. Sulfanilamide has given some responses but most in the active or early latent stage. When the indication arises this drug could be given during the pregnancy.

CONCLUSIONS

The findings from this small number become more impressive when the infrequency of the disease of lymphogranuloma venereum in association with pregnancy is recognized. Tempting though it is, specific deductions must be guarded against until confirmation appears.

1. The common occurrence of pregnancy and the acute phase (systemic manifestation) must be extremely unlikely.

2. It remains unsettled what results may follow for the fetus or for the mother if an active infection is acquired during pregnancy.

3. Sterility is not necessarily related to the disease unless it resulted from a reaction in the gonads, tubes, or uterus, which seems to be unlikely.

4. The pregnancy should be carried to term unless therapeutic abortion becomes indicated for an obstetric or medical reason.

5. Colostomy may offer technical difficulty either in a possible obstruction or by contamination at delivery particularly if one resorts to cesarean section.

6. Pregnancy per se did not alter apparently the course of the disease.

7. There is the possible hazard of mismanaged labor if the pelvis is obstructed.

8. Nineteen babies born of and breast fed by mothers with a latent lymphogranuloma venereum have been normal and free from the disease.

9. Only one baby in 13 showed any evidence of passive transfer of antigenic bodies. In spite of 2 positive tests (on third and tenth days), the tests became negative within three months and so remained.

10. Tests in the newborn should be made with known dependable antigens and with more than one antigen. Tests shortly after delivery and again months later are indicated.

11. The placentas appeared normal grossly and the few examined microscopically showed no characteristic alteration.

12. It is hoped that others interested in this field will make observations in all stages of lymphogranuloma venereum for evidence of transmission to the fetus in utero or at parturition.

Dr. Edward W. Gray's assistance in examination of the infants is greatly appreciated.

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DISCUSSION

DR. EDWIN L. ZANDER, New Orleans, La.—We have made a study of the cases of lymphogranuloma venereum in Charity Hospital in the past two years. There were five cases on the colored service in 7,685 deliveries and none on the

white service in 3,973 deliveries. All women were delivered of live babies weighing from four to six and one-half pounds, with an average weight of five pounds one ounce. The six and one-half pound case required an episiotomy which was sutured with silkworm and healed without difficulty. Three of the five cases terminated thirty-two to thirty-six weeks and the other two at term. There was no record of any abortions in patients with lymphogranuloma venereum. We have noticed in one case an increase in the size of the vulvar masses during pregnancy.

The danger of delivery from below lies first in the possibility of trauma at delivery, and second, in the danger of puerperal morbidity. In four of these five cases morbidity was present.

A positive Frei test does not mean that active infection is present but that at one time the patient may have been infected. We must emphasize that the clinical picture must conform to the disease in order that a positive Frei may be accepted as of value. We have seen cases in which all the venereal diseases were present in one patient and for this reason a careful differential diagnosis is necessary, especially between lymphopathia venereum and granuloma inguinale. There have been delivered in this same period at Charity Hospital, ten cases of granuloma inguinale of which six had syphilis also.

All the babies born are at present alive and have shown no evidence of the disease. It seems possible, however, that, in cases of pregnancy with active disease, fetal infection could occur, for we know of a case reported by Dr. R. E. Arnell and diagnosed by Dr. J. K. Howles in which granuloma inguinale of the umbilicus occurred after delivery from below.

It does not seem that sterility per se is a part of the disease as witness the eighteen cases reported herewith, plus the five cases we have had in the past two years. Naturally sterility from occlusion of the vaginal tract is possible. The vaginal tract itself is not frequently involved because of poor lymphatic system, as this is essentially a disease of the lymphatic system.

DR. F. J. TAUSSIG, ST. LOUIS, MO.—Dr. Hesseltine's paper brings up the general problem of vulvar lesions complicated by pregnancy. We have in cases of granuloma venereum a condition of the external genitals, particularly of the rectovulvar septum, that presents a serious danger at childbirth. My experience dates back many years before the time when this disease was recognized as an entity and when we were still calling it tertiary syphilis. In my City Hospital service in these years I recall approximately three cases, one of which was permitted to deliver from below without any special precautions. It resulted in a tear of the rectum and a stenosis that killed the patient. Where the disease is fairly well under control, it seems to me that the possibility of delivery from below is to be considered, provided we do not let the head go down on the pelvic floor, but proceed at once, after complete dilatation of the cervix, with a high perineotomy. This should be so high as to relieve all pressure against the rectovaginal septum, which, if involved, is likely to break through and cause a rectovaginal fistula. In cases of extensive involvement cesarean section is definitely indicated.

May I say just a word as to the tendency to do cesarean section in patients who have had a previous vulvectomy for leucoplakic vulvitis or carcinoma of the vulva. I have had several cases in this classification and I would say that cesarean section is practically never indicated, particularly if at the time of the vulvectomy care is taken to bring down a flap of the posterior vaginal wall, thus producing, at least in appearance, the condition of a second degree tear at the end of the operation. By bringing down the flap of the posterior vaginal wall, we prevent the stricture that otherwise results, and if in such cases we do a high perineotomy, we can apply forceps and obtain delivery without any complications from below.

DR. H. E. ANDERSON, OMAHA, NEB.—In 1939 we had one of these problems, which has been reported. The patient was a colored girl who had had a perirectal mass for a number of years during which time she had been delivered of two children. She had this very large perirectal mass when she came to us and also a slight elephantiasis of the vulva. While we were debating whether she should be sectioned, she underwent what was practically a precipitate delivery.

DR. HESSELTINE (closing).—In our series the morbidity was the same average as for the entire obstetric series. I might point out that these cases did not have much sloughing of the vaginal structures or, with one or two exceptions, open lesions. The worst one was a patient who had a therapeutic abortion and sterilization because of extensive vaginal sloughing. The others had a latent or a more or less completely healed process. It would be most interesting to learn what would be the results to the fetus if a systemic process developed.

NUTRITIONAL EDEMA IN PREGNANCY*

WITH AN ANALYSIS OF EIGHT SEVERE CASES

RUPERT E. ARNELL, M.D., F.A.C.S., AND WILLIAM F. GUERRIERO, M.D., F.A.C.S., NEW ORLEANS, LA.

(From the Departments of Obstetrics and Gynecology of the School of Medicine of Louisiana State University and Charity Hospital of Louisiana)

IN THE course of an extensive study carried out in the obstetric clinics and wards of Charity Hospital of Louisiana at New Orleans we have observed in considerable detail approximately 500 women who presented marked degrees of edema. In every instance the edema was too extensive to be classified as the type which appears so constantly in pregnancy that it might almost be described as physiologic. In the majority of instances it could be readily explained on the basis of cardiac or renal disease or the toxemias of pregnancy. In some instances it could be explained on the basis of miscellaneous causes, chiefly inflammatory or mechanical, such as thrombophlebitis, angioneurotic edema, or varicose veins. In a small group of cases the edema, which was very extensive, could not be explained on the basis of any of these causes.

In every one of the cases in this special group, a common factor of hypoproteinemia could be demonstrated and could be clearly attributed to protein malnutrition. In other words, the patients in this small group presented the type of edema which is classified as nutritional and which is due, alone or in combination, to an inadequate protein intake or to a deficient absorption or utilization of ingested protein.

The purpose of the present communication is to consider the association of nutritional edema and pregnancy, both in general and with particular reference to eight carefully studied cases in which the edema was

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of a very marked degree and was apparently conditioned primarily by a hypoproteinemia due to one or more of the causes listed.

A voluminous literature has accumulated concerning water balance and edema in pregnancy, and the nutritional aspects of maternal care have recently received a great deal of attention, but, so far as we have been able to ascertain, nothing at all has been published on the subject of nutritional edema in pregnancy. This is curious since, according to experienced workers in this field, nutritional edema is actually more frequent on the obstetric than on the medical services of most hospitals.

Historical Note.—The scientific study of edema due to malnutrition dates from 1865, in which year Cornish (cited by Nixon[1]) published his observations on the condition in India, where widespread famine had affected large portions of the population. As a matter of fact, this type of edema had been known for hundreds of years earlier and had always been associated with war or famine.

The Bible mentions the "hunger swellings" and "bitter end" of people suffering from famine after drought. In the fourth century B.C. the philosopher Heraclitus, according to Diogenes Laertius (cited by Youmans[2]), died of dropsy because he lived on a diet composed entirely of vegetables and herbs. Jovius wrote of the French army fighting before Naples in 1528, "Those starved soldiers who were not confined to bed were seen with pallid faces, swollen legs, and bloated bellies, scarcely able to crawl." Dozens of similar references might be cited in this connection.

The modern interest in nutritional edema dates from World War I, when, following the reduction of essential food supplies, numerous instances were reported, first in prison camps and devastated areas, and later in the general population. The first cases were observed at Lille, after the Germans, in 1914, had occupied the town and stripped it of its supplies. In 1918 Schittenhelm and Schlecht reported 200 cases from a single prison camp, and other large series were reported in that year and in the years immediately after the war.

In civil life nutritional edema has been reported from India, China, Ireland and Mexico, and has involved large proportions of the populations during periods of famine. It has been observed, in the absence of famine, in individuals with deficient diets, and is so frequent among the poorer classes of the United States that, according to Youmans,[4] it amounts to a public health problem.

Nutritional edema has long been recognized as a prominent clinical feature of such diseases as beriberi, scurvy, pellagra, typhus, dysentery, and malaria. When it appears in this association, some authors believe that it represents a special type of the particular disease with which it is associated.

Cornish stated that nutritional edema was a definite disease entity caused by a deficiency of nitrogenous foods. Many authors pointed out the association between the edema observed during the last war and the deficient diets prevalent then. Falta (cited by Youmans[2]), in 1917, stated that in the districts in which the disease was observed meat was frequently unobtainable for months at a time, and large

amounts of salt and water were ingested in an attempt to supplement the bread and thin vegetable soup which formed the chief items of the diet. Schittenhelm and Schlecht also noted the association between an excessively "wet" diet and edema. From the laboratory standpoint, Maver,[5] Schittenhelm and Schlecht, Falta and others studied the protein deficiency in the diet. Falta observed that the protein intake of the subjects whom he studied averaged less than 15 Gm. per day, and Maver found the serum protein of the blood low in instances of war edema. It was not until the past decade, however, that extensive clinical and experimental studies have clearly shown that the immediate cause of edema in these cases is a hypoproteinemia due to protein malnutrition of various origins.[6-9]

Maver, in 1920, was the first to recommend the term "nutritional edema" which is now in general use. Prior to that time the condition has been described by such terms as "famine edema," "war edema," "prison dropsy," "starvation dropsy," and "hunger swelling," all of which indicate the circumstances under which the edema may occur but give no hint of its etiology, as does Maver's nomenclature.

PATHOGENESIS AND ETIOLOGY OF EDEMA

Although much concerning the etiology and mechanism of nutritional edema remains to be elucidated, certain general statements concerning edema are applicable to this special variety, and are also applicable to nutritional edema in pregnancy. The special factors operative in pregnancy will be discussed under a separate heading.

Generally speaking, any type of edema occurs as the result of a complex mechanism dependent primarily on the following factors, which may occur alone or in combinations of two or more: (1) A decreased colloid osmotic or oncotic pressure of the plasma proteins, (2) an increased capillary permeability, (3) an increased capillary blood pressure, (4) a decreased lymphatic drainage and a decreased tissue pressure.

Nutritional edema is due to a protein deficit caused, as has been pointed out, by a deficiency of protein in the diet or by the loss or deficient utilization of ingested protein. Other causes also play more or less important roles. Anemia is very commonly found in association with the hypoproteinemia in such cases. Secondary or contributory factors include hot weather, overwork, the excessive ingestion of salt and water, the dependent position, and decreased elasticity of the tissue spaces. The effect of these various factors upon the mechanism responsible for edema should be briefly discussed.

Serum Protein Concentration and Colloid Osmotic Pressure.—The serum protein concentration of the blood chiefly determines its colloid osmotic pressure. Serum proteins are therefore the determining factors in the distribution of extracellular fluid. Albumin plays a more important role than globulin, because its osmotic effect is approximately four times greater.

Edema is likely to occur whenever the colloid osmotic pressure of the serum proteins is less than 20 cm. of water, at which level the serum protein concentration is usually less than 5.5 Gm. per cent and the serum albumin concentration is less than 2.5 Gm. per cent. On the other hand, no categoric statements can be made concerning the level at which clinical edema will appear; because of the variability of the other factors taking part in the phenomenon, there is no critical level of serum protein concentration, and each case must be studied individually. In serial determinations on a large number of pregnant women, we have frequently observed values as low as 4.9 Gm. per cent without associated pitting edema or abnormal weight gains.

Although nutritional edema is beyond question due to the adverse effects of a protein deficit, however it may be caused, on the osmotic balance, the so-called "lack loss" theory is an over-simplification of the subject. It does not, moreover, explain all cases, as various authors have pointed out. Whipple[10] has suggested that the liver may be concerned in a specific mechanism for the regeneration of plasma proteins, and that this mechanism may be disturbed by severe hepatic disease with resulting perversion of hepatic function. Such a theory would be supported by our recent observation of a case of acute yellow atrophy of the liver in pregnancy, in which the serum protein concentration did not at any time rise above 2.6 Gm. per cent, in spite of a very high protein intake and repeated blood transfusions. Casten and Bodenheimer[11] mention a similar case.

Relationship of Edema and Anemia.—It is now well known that severe anemia may cause edema, either per se or in association with hypoproteinemia. Peters and his associates[7] have demonstrated that when the two conditions co-exist, the edema will appear at higher protein concentrations than when hypoproteinemia alone is present. The mechanism of the production of edema associated with anemia is not clearly understood, though the anemia, as under all other circumstances, is caused by a deficiency in either the protein or the iron of which the hemoglobin molecule is composed.

A reasonable supposition is that an oxygen deficit may play a part. Casten and Bodenheimer pointed out that the anoxemia resulting from severe anemia may affect adversely the structures concerned with the synthesis of plasma proteins, producing, in turn, a hypoproteinemia and a decreased colloid osmotic pressure.

That anemia may be responsible for the appearance of edema, without an associated hypoproteinemia, is evident from the following cases which are of particular interest:

A white woman, 34 years of age, para vi, was admitted to the New Orleans Charity Hospital in the sixth month of pregnancy, suffer-

ing from hookworm associated with massive edema. The blood pressure was 135/90. The urinalysis revealed nothing abnormal. The initial examination of the blood revealed 910,000 red cells per c. mm. The hemoglobin value was 2.4 Gm. per cent and the cell volume 10.2 volumes per cent. The serum protein concentration was 6.4 Gm. per cent.

The patient received in all nine transfusions, totaling 5,150 c.c. of whole blood. Laboratory studies twenty-four hours after the second transfusion showed all the blood values elevated over the initial values. The red blood cells now numbered 1,680,000 per c. mm., the hemoglobin determination was 4.1 Gm. per cent, the cell volume 17.5 volumes per cent, and the serum protein concentration 6.8 Gm. per cent. Clinical improvement paralleled the laboratory improvement. Within twenty-four hours after the second transfusion the patient passed 6,200 c.c. of urine, and her weight loss in twenty-two days amounted to 17 kg. (37.4 pounds).

In this case the anemia was clearly the important factor in the abnormal water retention, and it is of interest to note the relatively small increase in hemoglobin, red cell count and cell volume which initiated the diuresis, weight loss, and general clinical improvement. Dieckmann[12] has also observed edema in a number of pregnant women who had serum protein concentrations well above the level at which edema would be expected to appear but all of whom exhibited varying degrees of anemia. In his cases edema was present when the hemoglobin values ranged from 3 to 8 Gm. per cent, but disappeared when the values had been increased to 11 Gm. per cent by blood transfusions.

On the other hand, too much should not be read into such cases, since anemia is not necessarily associated with edema or abnormal weight gain. We have observed several cases, for example, in which marked degrees of anemia, in one instance with a hemoglobin value of 4.4 Gm. per cent, was not associated with either of these findings.

Furthermore, when hypoproteinemia and anemia are associated, the hypoproteinemia may be the fundamental deficiency, as the following case (Table I), in which a deliberate therapeutic test was carried out, clearly shows:

A white woman, 31 years of age, para vi, was admitted to the New Orleans Charity Hospital in the eighth month of gestation, with massive edema of the extremities and trunk, which had been present for ten days. She also had a marked anemia and hypoproteinemia. For the first seven days of hospitalization general supportive measures were carried out, including bed rest, a high-protein, salt-poor diet, parenteral vitamin therapy, and intravenous hypertonic dextrose infusions. The response to these measures was slight. During the next six days the patient was given three transfusions of washed red blood cells. The anemia was strikingly benefited, but the edema was not materially improved and the serum protein concentration was only slightly altered. The patient was then given one transfusion of plasma and two of whole blood, which were followed by prompt results in respect of diuresis, improvement in and finally disappearance of the edema, and a loss of weight which by delivery had amounted to 16 kg. (35.2 pounds).

TABLE I. DEMONSTRATION OF ETIOLOGIC FACTOR (HYPOPROTEINEMIA VERSUS ANEMIA) IN CASE OF NUTRITIONAL EDEMA BY EFFECT OF VARIOUS THERAPEUTIC MEASURES

DATE	SERUM PROTEINS*		BLOOD			WEIGHT IN KG.	THERAPY
	TOTAL	ALBUMIN	CELL VOLUME	HEMOGLOBIN*	RED BLOOD CELLS†		
8/13/40	4.5	2.2	28.6	7.7	2.85	73.0	Bed rest, high-protein, salt-poor diet,
8/15/40	4.4		26.0	7.5		73.5	diet, intravenous dextrose (20%),
8/19/40	4.9			7.7		72.0	vitamins B_1 and C.
							Edema unchanged
8/20/40						71.0	Transfusion (red blood cells only, 250 c.c.)
8/21/40			30.2		3.10		Same (300 c.c.)
8/25/40	4.8	2.5		8.8		70.4	Same (250 c.c.)
9/ 1/40			32.9	9.4		68.8	Edema practically unchanged
9/ 3/40			32.5	9.0	3.65	69.0	Transfusion (plasma only) 250 c.c.
9/ 5/40	5.0		31.6	8.8		66.1	Edema improved
9/ 9/40						64.0	Transfusion (whole blood, 650 c.c.). Edema improving
9/10/40							Transfusion (whole blood, 500 c.c.). Edema improving
9/14/40	5.8	3.2	34.2	10.2	4.10	57.6	Edema entirely gone
9/27/40	6.9		37.4	11.0		57.0	Delivery

*In Gm. per cent.
†In millions.

Contributory Causes of Edema.—The influence of certain contributory causes of nutritional edema may be briefly mentioned. The observation that latent or mild edema becomes much more marked on very hot days is explained by the fact that in hot weather there is always peripheral vasodilatation, an elevation of the capillary blood pressure, and, as a result of capillary dilatation, an increase in the area of the capillary wall available for filtration, all of which add up to a disturbance of osmotic balance. This observation, as might be expected, is very common in the prenatal clinics of the New Orleans Charity Hospital.

The importance of an increased intake of salt and water, or their impaired elimination, or both, is now so well known in the pathogenesis of edema as to require no amplification. These factors, like the one just mentioned, are of unusual importance in the South, where highly seasoned food is the rule and where the ingestion of large amounts of salt, at times as high as 30 or 40 Gm. per day, is not at all uncommon and is an obvious source of danger for patients with potential or actual edema.

Another possible source of danger for such patients is found in what amounts to baking soda addiction. Among negroes in particular, baking soda is a household remedy, taken orally on all possible occasions, and pregnant women sometimes consume incredibly large amounts.

Both the dependent position of the extremities and strenuous physical activity of any kind increase the tendency to edema by increasing the capillary blood pressure. As Keys and Taylor[13] have pointed out, the hemoconcentration which occurs during activity is the result of filtration of fluid of low protein content from the blood into the tissues.

One of our patients stated that she had had only mild edema until she spent several days on her feet in a hot kitchen cooking and baking in preparation for her daughter's wedding. In another case the effect of dependency on both hematocrit and serum protein concentration could be demonstrated in the laboratory.

A colored woman, 28 years of age, para iv, presented a massive edema of the trunk and lower extremities for which a high Fowler position was necessary. Blood from the veins of the foot revealed the serum protein concentration to be 5.0 Gm. per cent, as compared with 4.1 Gm. per cent for the veins of the arm, and the hematocrit value to be 38.8 Gm. per cent for the veins of the foot as compared with 30.8 Gm. per cent for the veins of the arm.

NUTRITIONAL EDEMA IN PREGNANCY

The general statements which have been made concerning edema in general and nutritional edema in particular naturally apply to preg-

nancy also. In this state, as in any other state, hypoproteinemia may develop from an inadequate intake of protein, a deficient utilization of protein, or an excessive loss of protein because of vomiting, diarrhea, or proteinuria. Anemia and the other causes which have been discussed play parts of varying importance. Certain peculiarities of the pregnant state may also be mentioned.

Among these peculiarities are the physiologic alterations found in the latter part of pregnancy, which include, in addition to the mechanical effects of the enlarging uterus, an increase in blood volume amounting to 25 per cent; a decrease in plasma protein of 5 per cent; an increase in cardiac output of 50 per cent; and a moderate elevation in venous pressure.

Burwell[14] has demonstrated that the pitting edema of the ankles, usually found to some degree in most pregnant women late in gestation, may be attributed to increased venous pressure. According to Davis,[15] even a normal pregnancy is accompanied by a positive water balance, the fluid retention being most pronounced in the last trimester.

Melnick and Cowgill,[16] as the result of experiments on pregnant dogs, state that protein reserves are always decreased in pregnancy, that fetal demands on the maternal organism are always high, and that the mechanism of protein synthesis and regeneration is almost routinely impaired.

If these observations could be confirmed on human subjects, they would be an extremely important contribution to the subject of nutritional edema in pregnancy.

Site of Edema.—Under all circumstances the site of the edema is determined by the elasticity of the tissue spaces in various parts of the body. For this reason, as well as because of the mechanical conditions incident to pregnancy, the vulva, the tissues of which are very loose, is likely to become markedly edematous very rapidly.

In one instances of nutritional edema which we studied (Fig. 1), the vulvar edema was so marked that clear fluid could easily be withdrawn for chemical analysis. The local serum protein was 0.65 Gm. per cent and the chlorides 690 mg. per cent, as compared with the blood serum protein of 3.6 Gm. per cent, and the blood chlorides of 486 mg. per cent. The chlorides, which normally are only 40 or 50 mg per cent higher in the cellular spaces than in the blood, in this instance showed an increase of 204 mg. per cent.

This is a striking demonstration of the increased permeability of the capillaries to salt and water in pregnancy.

Dietary Deficiencies.—A protein deficiency might be expected in obstetric patients of the lower social stratum, but an investigation which we recently carried out on 100 pregnant women admitted consecutively to the prenatal clinics of the New Orleans Charity Hospital revealed deficiencies which were nothing short of startling. Almost without ex-

ception the diets were found to be deficient in proteins, minerals, and vitamins. The highest sustained protein intake was 1.4 Gm. per kg. of body weight per day, and the mean intake was 0.78 Gm., which is less than half the optimum intake for pregnancy (estimated at 1.5 to 2 Gm. per kg. per day for the last trimester of pregnancy). Sixty-eight per cent of the patients had intakes below the safe minimum and intakes of 0.3 Gm. per kg. per day were not at all unusual. With subclinical dietary deficiencies of such a degree, it is surprising that nutritional edema is not observed more frequently.

It must not be forgotten that dietary deficiencies are frequently present in private patients in easy financial circumstances. Patients of the poorer classes restrict their protein intake because foods which supply proteins of high biologic value cannot be secured on their limited in-

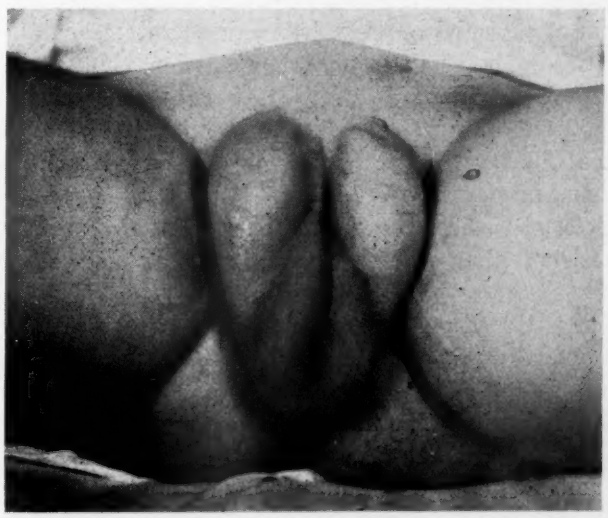

Fig. 1.—Case L. B. (Hospital No. L-48736.) Massive edema of the vulva in case of nutritional edema in pregnancy.

comes. Private patients restrict their diets because of food fads or actual or supposed idiosyncrasies to certain foods. In some instances the protein intake of pregnant women is still being restricted because of the idea, now completely disproved, that a high proportion of protein in the diet is likely to cause toxemia.

ANALYSIS OF CASES

Criteria of Selection.—The eight cases studied in detail upon which this paper is based were selected by criteria which were made deliberately high, in order to exclude questionable or borderline cases. These criteria included:

1. Absence of cardiac or renal disease, the toxemia of pregnancy, or any similar condition in which edema is a very frequent finding.

2. The presence of an obvious, deeply pitting edema of the lower extremities and vulva.

3. A minimum weight loss of 7 kg. (15.4 pounds) from the beginning of treatment to the day of delivery. The weight loss specified was selected arbitrarily, and was purposely made high, to avoid the criticism that it might have occurred as the result of other factors than loss of water. As a matter of fact, the weight loss was always greater than it seemed, since no allowance was made for the gain in weight which would normally be expected late in pregnancy.

Age, Parity, Race, and Stage of Gestation.—The youngest patient in the series was 26 and the oldest 41 years of age; the average age was 33 years. All the patients were multiparas, the parity ranging from 3 to 11 pregnancies. Observations on these and other groups of patients leave no doubt that the tendency to protein malnutrition is increased by the strain of repeated pregnancies in rapid succession.

The figures are too small to permit conclusions, but it may be mentioned that the predominance of white patients (5 white, 3 colored) may be significant, since 65 per cent of the obstetric admissions to the New Orleans Charity Hospital are colored patients. It seems reasonable to assume, in view of other information we possess concerning this race, that colored women, because of their habitually unbalanced diets, are more resistant than white patients to dietary defects during pregnancy.

In all 8 cases the edema was first noted in the last trimester of pregnancy. The stage of gestation when the patients were first seen was between twenty-nine and thirty-seven weeks, and the average duration was thirty-three weeks. The final trimester of pregnancy would be the logical time for nutritional disturbances to appear, since it is the time when both maternal and fetal requirements are highest.

Clinical Findings.—Edema was the only finding common to all cases, and in cases uncomplicated by other diseases or conditions was always the chief complaint. Weakness and dyspnea were observed frequently but not uniformly, and whether or not they were present seemed to depend upon the degree of edema or the presence of associated diseases. Physical examination, except for the edema, was essentially negative in every case.

All the patients had had edema of mild degree for several weeks, but the massive edema which brought them to the hospital appeared suddenly. It should be emphasized that none of them had ever had severe edema prior to its development at this time, and that the edema has not reappeared in any instance since the pregnancy, although the follow-up has been for periods ranging from six months to two years.

All of the patients had massive edema involving the lower extremities and trunk, and in some instances the upper extremities and face also. In every instance the edema about the vulva was particularly annoying.

It is a matter of interest that none of these patients contrary to the experience of others, who have studied hypoproteinemia, developed either ascites or pulmonary edema. Casten and Bodenheimer[11] point out that the lungs are so frequently involved in this type of edema as to seem a site of predilection.

The blood pressure was slightly elevated in two instances, to 150/90 and 148/85, respectively, and all the patients had rapid pulse rates when they were admitted to the hospital. The hypertension and elevation of the pulse rate promptly disappeared after the patients had been in bed for several hours, and could reasonably be attributed to the effects of dependency and physical activity, plus the increased effort required to move the swollen extremities.

Laboratory Findings.—Two patients had heavy traces of albumin in the urine, which disappeared soon after they were admitted. Urinalysis was essentially negative in the other six cases. Blood chemistry determinations, including urea nitrogen, nonprotein nitrogen, sugar, chlorides, cholesterol, and carbon dioxide-combining power, were all within normal range for the stage of pregnancy. Gastric analysis was carried out in three cases, one of which exhibited a hypoacidity. The Quick hippuric acid test revealed no hepatic dysfunction in the single case in which it was carried out. Roentgen ray examination of the chest and heart and electrocardiography revealed no significant findings. Examinations of the eye grounds were uniformly negative.

Anemia was present in every case, being of the hypochromic variety in six and of the hyperchromic variety in two.

Hypoproteinemia.—For all practical purposes, all of the findings mentioned, except the blood studies, were negative. On the other hand, studies of the serum protein concentration revealed it to be low in all eight cases (Table II), the principal decrease being in the albumin fraction. Calculations of the colloid osmotic pressure of the serum protein[17] gave values in all cases well below the level at which edema would be expected to appear.

TABLE II. SERUM PROTEIN VALUES AND COLLOID OSMOTIC PRESSURES IN EIGHT PREGNANT WOMEN WITH MARKED NUTRITIONAL EDEMA

CASE	SERUM PROTEINS*			ALBUMIN-GLOBULIN RATIO	COLLOID OSMOTIC PRESSURE†
	TOTAL	ALBUMIN	GLOBULIN		
1	3.0	1.6	1.4	1.14	9.3
2	3.6	1.8	1.8	1.0	11.6
3	3.8	2.1	1.7	1.23	12.9
4	4.1	2.0	2.1	0.95	13.7
5	4.4	1.9	2.5	0.76	14.5
6	4.5	2.2	2.3	0.96	15.6
7	4.8	2.5	2.3	1.08	17.5
8	5.4	2.2	3.2	0.70	18.6
Mean	4.20	2.03	2.16	0.94	14.21

*In Gm. per cent.

†Calculated in cm. H_2O by formula of Wells and others.[17]

Investigations of the diets of these patients revealed marked deficiencies in both the protein and the iron intake (Table III). Not one of the eight patients had an optimum intake (1.5 to 2 Gm. per kg. per day) and only one had an intake above the minimum subsistence level (0.8 to 1 Gm. per kg per day) for the last trimester of pregnancy. The highest daily intake was 0.9 Gm. per kg. of body weight, the lowest 0.28 Gm., and the average 0.54 Gm. Approximately a third of the total protein intake was derived from cereal and vegetable sources, which are of low biologic value, and in every instance the protein deficit had existed over a long period of time. In addition to the dietary deficiency, the hypoproteinemia was aggravated in six of the eight cases by vomiting, diarrhea, or the presence of other diseases, which resulted in either inadequate utilization or actual loss of the protein ingested.

The average iron intake in these cases, 9 mg. per day, is approximately 50 per cent of the optimum requirement and is relatively high when compared with the very low protein intake. The difference can be explained by the frequent use in this locality of such iron-containing articles of food as leafy vegetables, molasses, and sea food.

TABLE III. SERUM PROTEIN AND BLOOD VALUES IN RELATION TO PROTEIN INTAKE AND OTHER FACTORS IN EIGHT PREGNANT WOMEN WITH MARKED NUTRITIONAL EDEMA

CASE	SERUM PROTEINS*		BLOOD			[redacted]	ASSOCIATED CONDITIONS
	ALBUMIN	TOTAL	HEMOGLOBIN*	RED BLOOD CELLS†	HEMATOCRIT	PROTEIN INTAKE‡	
1	1.6	3.0	7.0	2.80	24.0	0.28	Vomiting
2	1.8	3.6	5.5	1.50	18.0	0.90	Hookworm
3	2.1	3.8	4.8	1.30	14.0	0.75	Hookworm
4	2.0	4.1	9.0	3.45	30.8	0.50	
5	1.9	4.4	8.8	3.13		0.40	Colitis
6	2.2	4.5	7.7	2.85	28.6	0.60	
7	2.5	4.8	6.8	2.48		0.55	Malaria
8	2.2	5.4	8.9	3.80	26.0	0.35	Diarrhea
Mean	2.03	4.2	7.3	2.66	23.6	0.54	

*In Gm. per cent.
†In millions.
‡Per kg. of body weight per day.

The season at which the edema was first observed is of interest in connection with the dietary deficiency. One case was observed in December, one in March, one in April, and five between June and September. It has been repeatedly noted at the New Orleans Charity Hospital that diets are more likely to be inadequate, especially because of the omission of meat, in the early spring and in summer than at other seasons of the year, the reason being that there is considerable seasonal unemployment at these times, and the patients have less money to spend for food. Several patients attributed their condition directly

to inadequate diets; thus one patient said that while attending a relative during a long illness she had scarcely eaten at all for many days at a time.

From what has been said, it is reasonable to attribute the hypoproteinemia and anemia present in every patient in this group chiefly if not entirely to a subminimum protein and iron intake. It was not possible, however, in any individual case to correlate the degree of anemia with the iron intake, or to correlate the serum protein level or the hemoglobin level with the protein intake, or to correlate the serum protein concentration and the degree of anemia. It was possible roughly to correlate the serum albumin concentration and the degree of edema. Close correlation of the various factors could scarcely be expected in all cases because of individual differences in the impairment of absorption and utilization of the ingested protein and iron.

Diagnosis.—The correct diagnosis was not made in any instance in this series until the patient had been admitted to the hospital. Four patients entered with a tentative diagnosis of toxemia of pregnancy, two with a diagnosis of cardiac decompensation, and one with a diagnosis of nephrosis. The eighth patient had been treated for pernicious anemia with large parenteral injections of liver.

Diagnostic difficulties are to be expected in a condition in which the symptomatology and gross findings, as well as certain laboratory findings, simulate the symptomatology and findings in other diseases. It is perfectly possible, furthermore, for nutritional edema to coexist with other diseases and conditions, such as vomiting or diarrhea from any cause, hookworm disease, amebiasis, cardiac or cardiorenal disease, and even the various toxemias of pregnancy. Edema is a clinical manifestation of many of these diseases, but it may be aggravated and intractable because of an associated nutritional factor, which should always be considered as a possibility, particularly when there is an inadequate response or no response to the therapy of the special disease. In our personal experience, swelling of the vulva, such as was apparent in these eight cases, is very unusual in obstetric patients unless it is associated with an acute nephritis or the nephrotic syndrome, both of which can readily be excluded. This observation may be of diagnostic aid.

Therapy.—Measures adequate in the treatment of latent or mild nutritional edema were not, of course, applicable to any of the cases included in this series, all of which were treated according to the following general plan:

1. The patients were put to bed at once. As has been pointed out previously, the general improvement observed in them all after even a few hours of bed rest is direct evidence of the bad effects of dependency and of the physical strain required for the movement of massively swollen extremities.

2. Dextrose infusions were given, for their nutritive value, their effect on the liver, and their diuretic effect. Diuretic drugs have not proved effective in our hands.

3. Vitamins B_1 and C were administered parenterally, on the empiric basis of possible deficiencies of these accessory factors in the diet, such deficiencies have not been proved in nutritional edema, but some observers still believe vitamin therapy to be of value.

4. When swelling about the vulva was a source of great discomfort, as it was in several cases, temporary relief was obtained by puncture of the swollen labia, under strict aseptic precautions.

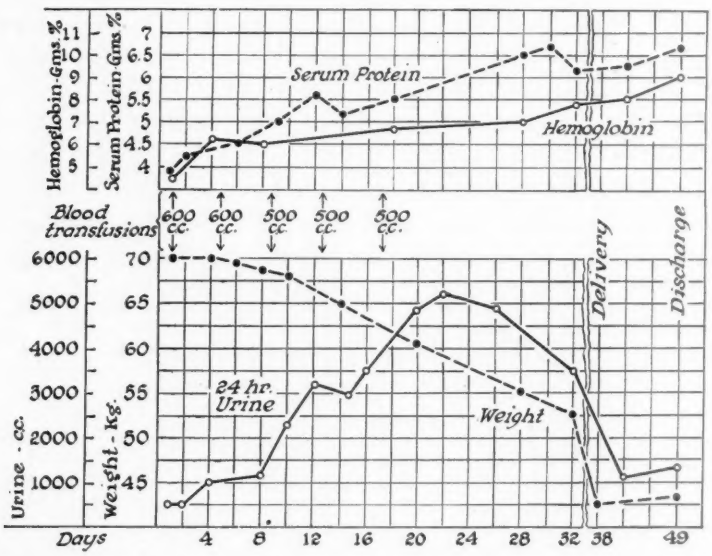

Fig. 2.—A. E. (Hospital No. L-40-15460.) Graph illustrating the typical response in weight loss, polyuria, increased serum-protein concentration, and hemoglobin value, following repeated whole blood transfusions in nutritional edema.

5. A high protein diet was instituted in all patients in whom digestive disturbances did not contraindicate oral feeding. Regardless of the digestive status of the patient, however, extreme protein deficiencies such as were observed in this group of cases cannot be corrected entirely or even chiefly by oral feeding.

6. The most important therapeutic measure in hypoproteinemia of this degree proved to be the use of transfusion, in the form of either whole blood or of plasma. Each patient received an average of four transfusions, totaling 2,000 c.c. of blood. The transfusions were given repeatedly, at fairly close intervals, and in large quantities, since no other method results in a sustained rise in the serum protein concentration. We observed elevations of as much as 0.5 Gm. following a single transfusion of 500 c.c. of whole blood, but never observed maintenance of the improvement unless additional transfusions were given without undue delay (Fig. 2).

The clinical improvement which followed even small elevations of the serum protein level in these cases furnishes added proof that there is no "critical level" at which edema appears or disappears. Clinical observation suggests that when the vicious cycle which produces edema is interrupted by raising the plasma protein concentration, thus increasing the plasma colloid osmotic pressure, a polyuria is produced which usually continues until the water balance is restored and the edema has completely disappeared.

At the beginning of the treatment whole blood is more desirable than plasma, because of the anemia frequently associated with hypoproteinemia. After the anemia has been corrected, the use of plasma is more desirable, for several reasons besides the obvious one that there is no point to overloading the circulation with red blood cells which are not needed. Plasma can be stored indefinitely without deterioration, and therefore is always available. It can be used without typing. It causes a minimum reaction. Finally, a given amount of plasma contains a much greater quantity of protein than does the same amount of whole blood; it has been estimated that 500 c.c. of plasma contains about 40 Gm. of protein, as compared with only 18 Gm. for the same amount of whole blood.

Cantarow[18] and Weech and his associates[19] do not believe that it is practicable to correct the protein deficit in patients with edema due to hypoproteinemia by the use of whole blood or of plasma or serum transfusion because these measures produce only a relatively slight rise in the serum albumin concentration. This has not been our experience. The elevation is frequently much greater than one would theoretically expect, and the good results can possibly be explained by the stimulating effect of the administration of protein on the endogenous mechanism for protein regeneration and synthesis. We have observed a similar stimulating effect when blood transfusions are administered in anemia or when hypertonic dextrose solutions are used for the relief of edema in the toxemias of pregnancy.

7. Human ascitic fluid, advocated by Davis and White[20] as a substitute for blood or plasma, was used in one case in this series, but the reaction was so severe that we did not feel justified in using this method again. We did not employ any of the various other measures suggested to increase serum protein concentration, including concentrated plasma[21] or serum[22] (both of which would undoubtedly be of value), essential amino acid mixtures,[23] or gum acacia.[24]

Results.—The average length of treatment in these eight cases was seventeen days. During this period, the average weight loss was 8.5 kg., and the range 7.4 to 19 kg. All the patients were free from pitting edema prior to delivery.

The average serum protein at delivery was 6.8 Gm. per cent, as compared with 4.20 Gm. per cent when the patients were admitted; the range at delivery was 5.8 to 7.5 Gm. per cent, as compared with 3.0 to 5.4 Gm. per cent on admission. The average hemoglobin at delivery was 10.2 Gm. per cent, as compared with 7.3 Gm. per cent on admission, and the average red blood cell count was 3,650,000 per c. mm. at delivery, as compared with 2,660,000 on admission.

There were no maternal or fetal deaths. The average weight of the children was 3.6 kg. (7.92 pounds). None of them had demonstrable edema or exhibited any other abnormality, and their serum protein and blood values were within normal limits.

SUMMARY AND CONCLUSIONS

1. Nutritional edema is due to a protein deficit caused by a deficiency of protein in the diet or by the loss or deficient utilization of ingested protein. It is frequently associated with anemia. Contributory factors include hot weather, overwork, the excessive ingestion of salt and water, and the dependent position.

2. In pregnancy, the protein demands of the organism are increased far above normal, and cannot be met by a patient suffering from a chronically lowered protein reserve. A state of hypoproteinemia therefore results, and is manifested clinically as so-called nutritional edema. The time of the appearance of the edema, its degree and site, and its final disappearance are dependent on a number of other factors, of which anemia is probably the most important.

3. The etiology of nutritional edema determines the corrective therapy, which includes, in severe cases, general measures, such as bed rest, dextrose infusions, and the parenteral administration of vitamins B_1 and C; and specific measures, such as a high protein diet and the replacement of the serum proteins by transfusions of plasma or whole blood. If anemia is present, its correction is of great importance, but will be inadequate for the relief of the edema until the associated hypoproteinemia is also corrected.

4. This paper is based on a detailed study of eight patients in the last trimester of pregnancy, all of whom exhibited marked nutritional edema associated with hypoproteinemia and anemia. They were selected, by very strict criteria, from a group of approximately 500 pregnant patients with edema of various origins.

5. These eight patients, as well as 100 other pregnant patients studied from the standpoint of dietary intake, all revealed very marked protein, iron, and vitamin deficiencies. It would, therefore, seem that adequate prenatal care should include a careful dietary survey, with particular emphasis on these elements of the diet, and the prompt correction early in pregnancy of any dietary deficiency. Since impairment of the digestion, with associated impairment of absorption and utilization

of the dietary intake, is common in pregnancy, due allowance should be made for these losses in estimating the nutritional intake. Various diseases, infections, and infestations which cause rapid protein deficits should also be taken into consideration, as should an associated anemia.

6. Pregnant women should ingest a diet adequate in protein. The protein should be in a readily assimilable form, should be from animal as well as from cereal and vegetable sources, and should contain the necessary amino acids.

7. Incipient and mild cases of edema due to hypoproteinemia, if recognized promptly, usually respond satisfactorily to correction by an intensive use of the dietary measures suggested. The diet, in addition to being high in protein content, should also be high in carbohydrates, because of their caloric value, their protein-sparing action, and their beneficial effect on the liver. The restriction of sodium is advisable, and bed rest is helpful.

We wish to express our appreciation to Dr. William J. Dieckmann of the Chicago Lying-in Hospital for many helpful suggestions during the course of this study.

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SYPHILIS IN OBSTETRICS*

E. D. Plass, M.D., Iowa City, Iowa

With the Assistance of Naomi Sacks, A.B.

(From the Department of Obstetrics and Gynecology, State University of Iowa)

OBSTETRIC syphilis has been so thoroughly studied and widely discussed that many phases of the problem can be considered settled for all practical purposes. There are, however, some particulars upon which there is no general agreement, and it is the purpose of this communication to analyze University Hospital Obstetric Service data which bear upon certain of these controversial issues.

GENERAL DATA

There were 400 women among approximately 11,000 admitted between Jan. 1, 1926, and Dec. 31, 1938, who were definitely syphilitic or who were strongly suspected of having the disease, and were therefore included in the analysis, an incidence of 3.6 per cent. One hundred and forty-four women, 36.0 per cent, were primigravidas, while 256 had been pregnant previously. Among the latter, 67 had been delivered in the Hospital on one or more previous occasions, and 55 were known to have been syphilitic at the time of the previous admission. The data, consequently, concern 345 individuals. The age range was from 14 to 43 years, with the median at 23 years. Three hundred and fifty-nine patients were white, 35 colored, and 6 Mexican. The latter two groups showed an incidence of syphilis from four to six times that of the white women.

Table I. Obstetric Syphilis—General Data

University Hospital (S. U. I.)—Jan. 1, 1926, to Dec. 31, 1938

Individual patients admitted	approximately 11,000		
Patients with syphilis	400		
Incidence	3.6+%		
Individual patients delivered	10,086		
Patients with syphilis	366		
Incidence	3.6 %		
Primigravidas	144	Single	92
Multigravidas	256	Separated	18
White	359	Divorced	13
Colored	35	Widowed	3
Mexican	6	Probably illegitimate	126
		Married	274

*Presented at the Thirteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, New Orleans, La., October 2 to 4, 1941.

SOCIAL DATA

Ninety-two, 23 per cent, of the syphilitic women were "single" as contrasted with an incidence of 14 per cent of single women among the total admissions. Moreover, 18 other patients were "separated," 13 "divorced," and three "widowed," and probably pregnant illegitimately, thus bringing the total of probable illegitimate pregnancies to 126, or 31.5 per cent.

TABLE II. 400 SYPHILITIC PATIENTS AMONG 11,000 PREGNANT WOMEN OBSERVED BETWEEN JAN. 1, 1926, AND DEC. 31, 1938

Discharged undelivered (outcome unknown)	32
Admitted with live baby shortly after delivery	2
Died in hospital undelivered	2
Delivered in hospital	364
Total	400
Incidence of syphilis, 3.6+ per cent	

Two hundred and one (50.3 per cent) of the 400 syphilitic women resided in urban centers (more than 10,000 population), which had only 30.4 per cent of the state population according to the 1940 census.

Three hundred and seventy-five patients were indigent, and 9 were "cost" patients. There were no syphilitic private patients, although this group represented 3.7 per cent of the total admissions.

CLINICAL DATA

The diagnosis of syphilis was made on the basis of positive serologic reactions (277 cases), or upon suggestive physical findings and definite history of infection (123 cases), including 54 doubtfully positive and 69 negative blood serologic reactions. In many instances the diagnosis had been made during a previous hospital admission. More than three-quarters of the women (305) had "latent" syphilis, while 13 had congenital, 27 early, and 15 late syphilis. In the 11 instances where the stage of the disease was not stated, it may fairly be assumed to have been latent.

FATE OF THE FETUSES

Exclusion of the 32 women who were discharged undelivered and of the two who died in the Hospital before parturition leaves 366 pregnancies terminated under observation. There were 5 sets of twins, which brought the total of observed fetuses to 371. Among this group were 14 abortions and 27 stillbirths, a total antepartum loss of 41, or 11.1 per cent. Three hundred and thirty children were born alive, but 14 (4.2 per cent) died during the neonatal period. The uncorrected fetal salvage, including children discharged alive and those transferred to the pediatric service, was 85.2 per cent. Exclusion of the 14 abortions raises the figure to 88.5 per cent.

TABLE III. 366 DELIVERED SYPHILITIC WOMEN, 5 SETS OF TWINS—371 FETUSES

Abortions (under 1,500 Gm.)		14
Spontaneous	11	
Criminal	2	
Therapeutic	1	
Premature (1,500 to 2,499 Gm.)		46
Discharged alive	22	
Stillborn	16	
Died in neonatal period	8	
Full-term (2,500 Gm. and above)		311
Discharged alive	294	
Stillborn	11	
Died in neonatal period	6	
Total		371

Total uncorrected fetal salvage, 85.2 per cent
Fetal salvage excluding 14 abortions, 88.5 per cent

The time when syphilis was contracted in relation to the pregnancy under consideration was known in 197 cases. The fetal salvage is greatest (89.4 per cent) when the original infection antedated the gestation but the small number of cases in the "at conception" and "after conception" groups makes the fetal mortalities hardly significant (Table IV).

TABLE IV. FATE OF FETUSES (371) IN RELATION TO TIME OF MATERNAL INFECTION

FATE OF FETUS	BEFORE CONCEPTION		AT CONCEPTION		AFTER CONCEPTION		NOT KNOWN	
Abortion	1		1		2		10	
Stillbirth	12		1		2		12	
Neonatal death	5		0		1		8	
Discharged alive	145		9		18		144	
Total	163		11		23		174	
	NO.	%	NO.	%	NO.	%	NO.	%
Abortions and premature births	18	11.0	2	18.2	6	26.1	34	19.5
Full-term births	145		9		17		140	
Discharged alive	145	89.4	9	81.8	18	78.3	144	82.8

Consistent with this evidence that time tends to attenuate the effect of maternal syphilis upon the children of an infected woman is the observation (Table V) that the highest fetal salvage occurred in the "latent" group and the lowest in those with early syphilis.

TABLE V. FATE OF FETUSES (371) IN RELATION TO STAGE OF MATERNAL SYPHILIS

FATE OF FETUS	CONGENITAL		ACQUIRED						NOT KNOWN	
			EARLY		LATENT		LATE			
Abortion	0		3		10		1		0	
Stillbirth	2		2		20		2		1	
Neonatal death	0		1		13		0		0	
Discharged alive	11		21		262		12		10	
Total	13		27		305		15		11	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Abortions and premature births	1	7.7	7	25.9	48	15.7	3	20.0	1	9.1
Full-term births	12		20		257		12		10	
Discharged alive	11	84.6	21	77.8	262	85.9	12	80.0	10	90.9

TABLE VI. FATE OF FETUSES (371) IN RELATION TO TIME OF MATERNAL TREATMENT

FATE OF FETUS	NOT TREATED BEFORE OR DURING PREGNANCY		TREATED BEFORE BUT NOT DURING PREGNANCY		TREATED DURING BUT NOT BEFORE PREGNANCY		TREATED BOTH BEFORE AND DURING PREGNANCY	
Abortion	8		1		5		0	
Stillbirth	7		5		12		3	
Neonatal death	9		1		1		3	
Discharged alive	54		32		144		86	
Total	78		39		162		92	
	NO.	%	NO.	%	NO.	%	NO.	%
Abortions and premature births	22	28.2	10	25.6	24	14.8	4	4.3
Full-term births	56		29		138		88	
Discharged alive	54	69.2	32	82.1	144	88.9	86	93.5

The most potent factor favoring fetal survival is antisyphilitic therapy during the pregnancy. Table VI shows that the fetal risk is five times greater when no treatment has been given than when therapy has been offered before and during pregnancy. Evidently treatment before conception, excepting only the instances in which the syphilis has been serologically cured, offers little protection to the child in a succeeding gestation. Among the 66 women with seronegative syphilis, the fetal survival rate was 89.4 per cent, or, excluding two early abortions, 92.2 per cent. Among the four stillborn children and the one who died in the neonatal period, only one, a premature stillbirth, showed any postmortem evidence of syphilis.

Abortion has been defined as the expulsion of a fetus weighing less than 1,500 Gm. and therefore generally previable. Using this criterion, there were 14 abortions, 3.8 per cent. In 9 instances, the fetus weighed more than 500 Gm., and in 6 cases more than 1,000 Gm. Only three of the 9 fetuses were subjected to autopsy, but they all showed lesions of congenital infection, and it is reasonable to assume that the others were infected except in one case where placenta previa was present and necessitated therapeutic measures which may have proved fatal to the fetus. Among the five early abortions there was one therapeutic intervention for pulmonary tuberculosis, two incomplete criminal miscarriages, and two spontaneous abortions at ten and sixteen weeks, respectively. No autopsies were performed but it seems doubtful whether the interruption of the pregnancy could in any case be attributed to the maternal infection.

Stillbirths occurred in 27 cases, 16 times in the premature classification (1,500 to 2,499 Gm.) and 11 times with children in the term group (over 2,500 Gm.). Autopsies were performed in 25 cases with a pathologic diagnosis of congenital syphilis in 7, and with spirochetes demonstrable in only 3.

Fourteen children died in the neonatal period, and 12 were subjected to post-mortem study, with 6 deaths attributed to congenital syphilis, although the spirochetes were demonstrated only in 3.

It would then seem reasonable to attribute 8 abortions, 7 stillbirths, and 6 neonatal deaths directly to the maternal infection, and to view the lethal effect of the syphilis with some scepticism in the remaining 34 fetal fatalities. This, however, leaves such a high fetal death rate (34 out of 371), unexplained by delivery complications or by other recognized factors, that a majority of them may be attributed to the direct or indirect effect of the maternal syphilis.

LIVING CHILDREN

Three hundred and sixteen children (85.2 per cent) were discharged alive or transferred (30) to the pediatric service more than ten days after birth. In the latter group there were 5 premature and 25 full-term children; 10 were proved to be syphilitic and 17 nonsyphilitic, with the diagnosis undetermined in three. Five of the entire group died while under treatment, but death was attributed to syphilis in only one, who is not considered further in this study. The other 4 deaths were attributed as follows: erysipelas one, congenital cardiac disease one, and prematurity two.

The diagnosis of congenital syphilis in newborn children is admittedly difficult in spite of the various tests which have been introduced to facilitate differentiation and to hasten the inauguration of proper intensive therapy when indicated. None of the procedures commonly used (cord blood or vein blood serologic tests, histologic examination of the placenta, and x-ray films of the long bones) has proved reliable; errors in both directions are common, and even the usually accepted physical signs of syphilis in the first weeks of life may prove misleading. On the other hand, complete reliance can evidently be placed upon blood serologic tests performed at the age of two or three months. Consequently, the syphilitic status of the liveborn children in this series was considered only when this evidence was available in later pediatric records or from other sources.

By reason of the difficulties inherent in the admission of the patients from the entire state of Iowa, it has been possible to follow only 118 children sufficiently long to determine whether or not they should be considered congenital syphilitics, and the following discussion will involve only this group. It is unfortunate that there is such a large group with "undetermined status" and it is futile to discuss them, although it would not be unreasonable to assume that the incidence of congenital infection would closely parallel that in the thoroughly studied series.

The status of the living children in terms of the type of maternal syphilis (Table VII) shows nothing unusual except that one child of

TABLE VII. STATUS OF LIVING CHILDREN IN RELATION TO TYPE OF MATERNAL SYPHILIS

TYPE OF MATERNAL SYPHILIS	CHILDREN BORN ALIVE	SYPHILITIC STATUS		
		SYPHILITIC	NONSYPHILITIC	UNDETERMINED
Congenital	11	1	2	8
Acquired, early	21	5	5	11
Acquired, late	12	0	4	8
Acquired, latent	262	31	69	162
No data	10	0	1	9

The syphilitic status was considered "undetermined" when there were no clinical evidences of infection before discharge, and when no follow-up examination and later serologic study were possible.

Undoubtedly many of the children in this group were syphilitic.

eleven born alive to congenitally syphilitic mothers itself had congenital syphilis. It is commonly accepted that third generation offspring do not acquire the disease unless the mother has an acquired syphilis in addition to the congenital infection.

This particular woman had had one previous child, who showed no evidence of syphilis. She had been treated adequately before the second pregnancy as well as during the entire gestation period. However, her vein blood was still positive and the second child was finally diagnosed as being syphilitic, although there were no physical signs or positive laboratory findings in the neonatal period. The patient's husband had an old, acquired syphilis, a fact which suggests the transmissibility of the maternal infection by way of the imposition of acquired syphilis upon the congenital infection. It was to have been expected that early syphilis in the mother would endanger the child more than a late or latent infection.

The presence of negative maternal blood serologic tests does not assure an uninfected child; in two instances such mothers gave birth to syphilitic infants.

Both the cord blood and neonatal vein blood serologic tests proved unreliable, more often by indicating that a child had congenital syphilis when further study showed it to be uninfected. This situation developed in connection with cord blood studies on 29 of 45 proved nonsyphilitic children, whose cord blood was studied, and in 19 of the 35 where vein blood was tested. Something more than one-half of the nonsyphilitic children would have been incorrectly diagnosed on the basis of these tests. It is also of interest that 5 of the congenitally syphilitic children had serologically negative cord blood and one showed a negative vein blood.

Other tests proved equally unreliable. Enlargement of the placenta to more than one-fourth of the child's birth weight was almost as common in the nonsyphilitic as in the syphilitic group, while the histologic changes supposedly characteristic of syphilis were found with 6 nonsyphilitic children as against one syphilitic child.

TABLE VIII. SEROLOGIC FINDINGS IN LIVING CHILDREN KNOWN TO BE DEFINITELY SYPHILITIC OR NONSYPHILITIC

NATURE AND RESULT OF TEST	SYPHILITIC (37)			NONSYPHILITIC (81)		
	PREM.	TERM	TOTAL	PREM.	TERM	TOTAL
Maternal vein blood:						
Neg.	0	2	2	1	4	5
Doubt.	0	1	1	0	10	10
Pos.	5	29	34	5	61	66
Babies' cord blood:						
Neg.	0	5	5	1	11	12
Doubt.	0	1	1	1	3	4
Pos.	1	15	16	1	28	29
N.D.*	4	11	15	3	33	36
Babies' vein blood†:						
Neg.	0	1	1	2	9	11
Doubt.	0	0	0	1	4	5
Pos.	4	13	17	0	19	19
N.D.	1	18	19	3	43	46

*N. D., No data; not determined.
†During first few days of life (neonatal period).

TABLE IX. OTHER FINDINGS IN LIVING CHILDREN KNOWN TO BE DEFINITELY SYPHILITIC OR NONSYPHILITIC

NATURE AND RESULT OF TEST	SYPHILITIC (37)			NONSYPHILITIC (81)		
	PREM.	TERM	TOTAL	PREM.	TERM	TOTAL
Placental weight:						
More than ¼	1	3	4	1	5	6
Less than ¼	4	29	33	5	70	75
Placenta:						
Histologic changes	0	1	1	1	5	6
Normal histology	1	9	10	3	34	37
N.D.	4	22	26	2	36	38
X-Ray, long bones:						
Neg.	2	12	14	4	40	44
Doubt.	0	3	3	1	11	12
Pos.	1	6	7	0	4*	4
N.D.	2	11	13	1	20	21

Only 6 syphilitic babies showed clinical signs of syphilis in the neonatal period. Two others had "snuffles" and one an enlarged liver, all later shown to be nonsyphilitic.

*Considered nonsyphilitic because of persistently negative serologic reactions.

X-ray examination of the long bones showed so many errors in both directions as to be practically useless; four nonsyphilitic children were interpreted as being positive, whereas 14 syphilitic children showed no long bone changes.

Only 6 of the 37 syphilitic children showed clinical signs of syphilis, —snuffles, skin lesions, and visceral enlargement; while two others with snuffles and one with an enlarged liver were later known to be uninfected.

Assuming the specificity of the various serologic tests for syphilis at the age of two to three months, as has been done here, it is obviously impossible to make an accurate diagnosis on a newborn child by any of the methods now available.

Whether or not it is justifiable to offer antisyphilitic therapy before a definite diagnosis is possible must continue debatable although probably little harm would ensue provided the therapy is not too energetic.

FATE OF THE MOTHER

There were four deaths among the 368 women cared for in the Hospital, and in each instance the fatality was directly attributable to antisyphilitic therapy, being due to arsenical encephalitis. Three of these cases have been reported previously, while the fourth occurred in 1937. In each instance, the fatal neurologic manifestations appeared after 2 to 6 neoarsphenamine injections of not more than 0.4 Gm., and death occurred in 24 to 36 hours. In three instances, the cause of death was confirmed at necropsy, while in the fourth the clinical picture was quite unequivocal.

In addition to these fatal reactions, there were 27 of less severity, as shown in Table X, among the 254 women treated in the hospital, a re-

TABLE X. TREATMENT REACTIONS AMONG 254 WOMEN TREATED DURING PREGNANCY

	NO.	PER CENT
Arsenical dermatitis	9	3.5
Local inflammatory reaction	8	3.1
Transient fever	5	2.0
Transient albuminuria	4	1.6
Arsenical encephalitis	4*	1.6
Arsenical hepatitis	1	0.4
Total	31	12.2
Treatment mortality	1.6%	

*All four patients who developed arsenical encephalitis died, the only deaths in the series.

action incidence of 12.2 per cent. The fatality rate among the treated patients was 1.6 per cent, while other severe reactions (dermatitis and hepatitis) were present in an additional 3.9 per cent. Since the end of the period included in this survey, an additional death evidently due to arsenical poisoning has been observed. This patient, a primigravida, aged 15 years, received 10 doses of 0.3 Gm. arsphenamine over a period of twenty-one days. About halfway through the series smallpox vaccination was done and resulted in a take with several areas of secondary inoculation on the face, vulva, and breast. A few hours after the tenth arsphenamine injection the patient had a chill and then started in labor. She was delivered spontaneously the following day and died eighteen hours later. During the last two days of life the leucocyte count fell from 13,400 to 600 with no granulocytes. Autopsy showed acute pulmonary edema and lobular pneumonia, with blood and marrow evidence of agranulocytosis.

Experiences of this character appear to be unusual on the basis of reports in the literature, although there is an occasional suggestion that arsenical therapy may not be tolerated so well in pregnancy as in the

male and in nonpregnant women. There is no plausible explanation for this high percentage of fetal reactions, since the doses have not exceeded those commonly recommended and the treatment intervals have not been too short.

SUMMARY

Syphilis is an obstetric problem of considerable significance among patients in the lower economic groups, even in a predominately rural state such as Iowa, where most of the people are native born whites.

The fate of the offspring of syphilitic women appears to depend less upon the duration of the infection at the time of conception and previous antisyphilitic therapy than upon the character and extent of treatment during pregnancy. The best results are obtained when treatment during pregnancy follows anteconceptional therapy.

None of the diagnostic measures available makes possible the determination of the syphilitic status of the child of a syphilitic woman during the neonatal period. Standard serologic tests are practically pathognomonic at the age of two or three months and are alone to be depended upon.

The syphilitic pregnant woman appears especially likely to develop treatment reactions to the arsenical antisyphilitic drugs, which should, therefore, be used with caution.

DISCUSSION

DR. JAMES R. REINBERGER, MEMPHIS, TENN.—While sufficient attention has been devoted to the care of the unborn, too little interest has been directed toward ill effects of syphilitic therapy. Dr. Plass's presentation of such ill effects in his article, "Hemorrhagic Encephalitis Following Intravenous Arsphenamine," centered my attention upon this subject in 1935. Since that time three recognized deaths from such causes have occurred on the obstetric service of the John Gaston Hospital of the University of Tennessee, five additional cases with severe reaction have also been recorded.

In an effort to compare the frequency of fatal accidents among all patients receiving neoarsphenamine in the John Gaston Hospital with the incidence of deaths from this drug during pregnancy, I found that there were 15 deaths in the 91,441 patients admitted to the hospital during the years 1935 through 1940, against 3 deaths in 13,316 obstetric patients admitted during these same years. In other words about one patient died in 4,453 in the pregnant; and, 6,096 in the nonpregnant. This would indicate that there is not more susceptibility in the pregnant patient. A review of such deaths showed very definitely, however, that the minor reactions to arsenic in all of its compounds are too often overlooked until a major catastrophe results from continued treatment.

The end results in the treatment of the syphilitic mother or in the newborn baby were in general the same as those presented by Dr. Plass. In a series of 1,000 consecutive cases of syphilis in pregnancy, reported by Reinberger and Toombs in *The Southern Medical Journal* in 1933, it was found that, despite treatment, there were 35 per cent of syphilitic tragedies including abortion, premature labor, stillborn and infected newborns. This study stressed moreover:

1. that antisyphilitic treatment is indicated in each case;
2. that the earlier treatment is begun, the more unlikely syphilitic tragedies;

3. that pregnancy does not alter the Wassermann reaction;
4. that serologic more often than clinical evidence is present in the treated infected newborn infant;
5. that antisyphilitic treatment is indicated in every pregnant woman ever known to have syphilis, irrespective of her present serologic or clinical findings; and
6. that despite most intensive therapy syphilitic tragedies must be expected in some cases.

A REVIEW OF SEVENTY-FIVE CASES OF ECLAMPSIA*

With Particular Reference to Late Cardiovascular Renal Effects

G. Sydney McClellan, M.D., W. D. Strayhorn, M.D., and Paul M. Densen, D.Sc., Nashville, Tenn.

(From the Departments of Obstetrics and Gynecology, Medicine, and Preventive Medicine and Public Health, Vanderbilt University School of Medicine)

INABILITY to determine a specific cause for the toxemias of pregnancy has resulted in an attempt to explain them in relation to known cardiovascular renal diseases, such as hypertensive vascular disease, vascular nephritis, and acute or chronic glomerulonephritis. This trend is obvious in recent years in the writings of both obstetricians and internists who have become interested in these special problems of obstetrics. Many authors have held the view that an unduly high proportion of women who have had toxemia during pregnancy will later in life be found to have hypertensive vascular or renal disease.

This paper represents a preliminary study of observations made on seventy-five patients who were diagnosed as having eclampsia in the Vanderbilt University Hospital during the past fourteen years. An attempt has been made to determine, where later information was obtainable, the presence or absence of hypertension, vascular or renal disease, and the present discussion is chiefly concerned with this phase of the problem. The diagnosis in the cases under discussion has been made on the basis of the development of hypertension and convulsions in the last trimester of pregnancy where there was no evidence of chronic renal disease.

Of the 75 cases, 49 were primiparas and 26 were multiparas. This ratio of a little less than 2 to 1 is lower than is given in other reports.[1, 7] The ages of these patients were from fifteen to forty-four years with 86 per cent of the primiparas and 27 per cent of the multiparas below twenty-five years of age.

Of the 26 cases of eclampsia among the multiparas, 11 occurred during the second and third pregnancies. Two occurred in women who had been pregnant ten or more times.

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MATERNAL MORTALITY

The immediate maternal mortality was 13.3 per cent. Ten of these patients died in the hospital. One of them died of pulmonary emboli from a pelvic thrombophlebitis during post-partum convalescence. It is pertinent that none of these patients had received any prenatal care, and they were either moribund on admission to the hospital or went into profound shock following delivery. Those who were moribund had all the symptoms and signs of the severest type of eclampsia, such as coma, 10 or more convulsions, extremely high blood pressure, rapid pulse, and elevation of temperature. These facts support the viewpoint of many investigators that the earlier the disease is treated, the more favorable the prognosis.

Three of the patients who died had spontaneous deliveries and two were delivered by low forceps. Three of the 10 patients died undelivered. Two of the deaths followed cesarean sections. There were only 5 cesarean sections done among the 75 cases. This number is too small to justify any conclusion as to the advisability of using this treatment in eclampsia. However, it is generally agreed among authors that the surgical approach in the treatment of eclampsia is associated with a maternal mortality of from 23 to 48 per cent.[2, 3]

Of the 65 individuals discharged from the hospital only one is known to have died. This patient died at fifty years of age, ten years after an attack of eclampsia, from cardiac failure and pulmonary atelectasis following an operation for repair of an incarcerated ventral hernia in the site of a scar resulting from a cesarean section. An autopsy revealed generalized arteriosclerosis with benign nephrosclerosis, cardiac hypertrophy, and congestive failure. There was no evidence of glomerulonephritis.

OUTCOME IN THE FETUS

The gross fetal mortality for the group was 26.7 per cent. Included in the 20 deaths were 3 babies which were undelivered and 2 which died during the first week of life. There was no apparent relationship between the fetal mortality and the number of convulsions.

It is interesting to note that there were 3 sets of twins, making an incidence of 1 in 25 deliveries. This is about three times the average and follows the general conception that late toxemias are found more frequently associated with multiple pregnancy.[4-7]

RESULTS OF FOLLOW-UP

Follow-up observations were made on 42 of the 75 cases of eclampsia studied. It was decided, however, that no observations made less than six months post partum would be included in the following tabulations since most of these occurred between the fourth and eighth week post partum. The effect of this decision was to exclude 12 patients from

consideration. There remained 30 patients on whom 55 observations were made at varying lengths of time since the pregnancy in which eclampsia occurred. These 55 observations are shown in Table I.

TABLE I. LENGTHS OF FOLLOW-UP AFTER THE PREGNANCY IN WHICH THE ECLAMPSIA OCCURRED

YEARS SINCE PREGNANCY	NO. OF OBSERVATIONS
6 months to 1 year	11
1- 2 years	11
2- 3 years	6
3- 4 years	4
4- 5 years	2
5- 6 years	8
6- 7 years	3
7- 8 years	3
8- 9 years	1
9-10 years	–
10-11 years	3
11-12 years	–
12-13 years	–
13-14 years	3
Total	55

Table II shows the number of follow-up observations made in each age group and the number with systolic pressures of 140 mm. or more in the respective age groups. Thus, out of the 55 observations made at varying ages following the pregnancy in which eclampsia occurred, 11 were found to have a systolic pressure of at least 140 mm. It is difficult to obtain a series of observations to use as controls which are not selected in one form or another. Comparison is made in Table II with observations made by Saller[8] on women attending the outpatient clinic in Kiel, Germany; with Wetherby's[9] data for women in the Minneapolis outpatient clinic; with blood pressure readings made during a nutritional study[10] on a sample of the women living in Wilson County, Tennessee; and with observations before the third trimester on a group of presumably normal obstetric patients who returned to the outpatient service of Vanderbilt University Hospital with subsequent pregnancies.

For each of the four control groups, the percentage of observations showing a systolic pressure of 140 mm. or more was computed for each age group. These percentages were then applied to the number of observations in that age group of women who had had eclampsia. This yielded the number of observations which would be expected to have a systolic pressure of 140 mm. or more in each age group if the incidence of hypertension in the eclamptic group were the same as in each of the control groups. These expected values and their totals for all ages are shown in Table II.

Thus it is seen that if the incidence of hypertension in the post-eclamptic group were the same as found in Saller's and Wetherby's outpatient clinics 10 and 9 cases of hypertension, respectively, would be expected for the group as a whole. The number observed (11) was

TABLE II. COMPARISON OF OBSERVED AND EXPECTED NUMBER OF WOMEN AT CERTAIN AGES WITH SYSTOLIC PRESSURES OF 140 MM. OR MORE

AGE	OBSERVED DATA		NUMBER OF CASES EXPECTED IF THE INCIDENCE WERE THE SAME AS IN			
	TOTAL OBSERVATIONS	OBSERVATIONS 140 MM. OR MORE	SALLER'S OUTPT. CLINIC	WETHERBY'S OUTPT. CLINIC	WILSON CO. POPULATION	WOMEN WITH NORMAL PREG.
15-19	2	–	–	–	–	–
20-24	16	1	2	* 2	–	* 1
25-29	12	–	2		1	
30-34	9	3	1	* 3	2	* 1
35-39	9	1	2		2	
40-44	4	3	1	* 3	1	
45-49	1	1	1		–	
50-54	2	2	1	1	1	
Total	55	11	10	9	7	
Number of cases in control group			1,270	2,695	224	170

*Ten-year age period.

practically the same. It must be remembered, however, that there is a tendency for observations in outpatient clinics to be selected for relatively high blood pressures.

When comparison is made with the Wilson County population group it is seen that the incidence of hypertension among the post-eclamptics is slightly higher than would be expected; the comparable figures being 11 for the post-eclamptic group and 7 for the sample of Wilson County population. The difference, however, might very well arise solely as a matter of chance, and further observations are needed before one may say that the incidence of subsequent hypertension is greater among women who have had eclampsia than among the population in general.

No observations were made above the age of thirty-nine in the group of women with normal pregnancies. Five observations of 140 mm. systolic pressure or higher were observed in the comparable age groups, whereas only two would be expected. Here, however, the selection present in the control group is in the direction of low blood pressures. These findings are presented merely to obtain some idea of the relative position of readings on a group of women who have had eclampsia when compared with four groups such as those indicated.

Comparison of the incidence of diastolic pressures of 90 mm. or more between the post-eclamptic and the control groups is shown in Table III. In general, the findings are the same as were noted for systolic pressures.

Urine examination at the time of follow-up showed at least a two-plus proteinuria in only 2 of the 55 observations.

In addition to information obtained at the time of the follow-up examination on the above 30 patients, it was possible to contact 9 other patients by letter with regard to their subsequent pregnancies. Among these 39 patients, a total of 32 pregnancies were reported following the pregnancy in which eclampsia occurred. There was no recurrence of eclampsia in any of these later pregnancies.

TABLE III. COMPARISON OF OBSERVED AND EXPECTED NUMBER OF WOMEN AT CERTAIN AGES WITH DIASTOLIC PRESSURES OF 90 MM. OR MORE

AGE	OBSERVED DATA		NUMBER OF CASES EXPECTED IF THE INCIDENCE WERE THE SAME AS IN			
	TOTAL OBSERVATIONS	OBSERVATIONS 90 MM. OR MORE	SALLER'S OUTPT. CLINIC	WETHERBY'S OUTPT. CLINIC	WILSON CO. POPULATION	WOMEN WITH NORMAL PREG.
15-19	2	–	–	–	–	–
20-24	16	2	3	* 4	–	* 1
25-29	12	1	3		2	
30-34	9	2	2	* 4	1	* –
35-39	9	3	2		2	
40-44	4	3	1	* 2	1	
45-49	1	–	–		–	
50-54	2	1	1	1	1	
Total	55	12	12	11	7	
Number of cases in control group			1,261	2,695	224	170

*Ten-year age period.

DISCUSSION AND SUMMARY

In the last fourteen years 75 cases of eclampsia have been diagnosed in the Vanderbilt University Hospital. Forty-nine of these patients were primiparas and 26 were multiparas.

The immediate maternal mortality was 13.3 per cent. None of the patients who died had had any prenatal care, a fact tending to emphasize again the findings of other investigators that the earlier the disease is treated, the better the prognosis. Only one of the 65 individuals discharged from the hospital is known to have died. This individual was fifty years of age at the time of death, which occurred ten years after an attack of eclampsia.

In order to study the question of whether or not an unduly high proportion of women develop hypertension after having had an attack of eclampsia an attempt was made to follow up the patients studied. A total of 55 observations was made on 30 individuals. While the length of follow-up ranged from six months to thirteen years, half of the observations were made within three years. Because of the relatively small number of cases and because of the short length of follow-up, the present discussion should be considered a preliminary report.

The number of cases of hypertension which developed among the post-eclamptic patients was compared with observations made on the blood pressure of women attending outpatient clinics in Kiel, Germany, in Minneapolis, with observations made on a sample of the women living in Wilson County, Tennessee, and with readings before the third trimester on a group of women who returned to the obstetric outpatient service of the Vanderbilt University Hospital after having had a normal pregnancy.

In general, the evidence in this study does not indicate that individuals who have had attacks of eclampsia develop hypertension in any

undue proportion; however, further observations are required before any definite conclusion may be reached.

It should be pointed out that even if a high relationship is shown it does not necessarily mean an etiologic relationship. The very nature of eclampsia is such that one would suspect that its severe strain on the cardiovascular system might not only bring out a latent but even initiate hypertensive vascular disease.

Dieckmann and Brown[4] have summarized the literature on this subject. They find an average incidence of 27 per cent hypertension and 19 per cent chronic nephritis subsequent to attacks of eclampsia. In making comparisons, recognition should be taken of the possible lack of conformity in making the diagnosis of hypertension and chronic nephritis. Not all authors make a distinction between hypertensive vascular disease, vascular nephritis, and glomerulonephritis. One should also take account of the length of time over which the patients have been followed.

Teel and Reid[11] reported that a follow-up examination of patients who had had eclampsia showed an incidence of hypertension among all cases of 27.5 per cent. After 7.6 years, however, in the group known to have had normal blood pressure and urine previous to the pregnancy with eclampsia, the incidence was only 10.3 per cent. They found a higher incidence of hypertension in the nonconvulsive, mild toxemias than in eclampsias, and stated that "the commonly held viewpoint that eclampsia frequently causes permanent and progressive vascular or renal damage is not substantiated by our data."

There were no cases of chronic glomerulonephritis in our follow-up group and in none of the 32 subsequent pregnancies was there any recurrence of eclampsia. This finding supports the view of Dieckmann that the incidence of recurrence is inconsiderable.

The solution of as complex a problem as eclampsia requires the integration of a large number of laboratory, clinical, and epidemiologic observations. Adequate controls will need to be established and follow-up will require a sufficiently long time to allow full observation of after-effects. It is hoped that it will be possible to continue the present study to fulfill these requirements.

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DISCUSSION

DR. C. RAYMOND MAYS, SHREVEPORT, LA.—We have an abundance of eclamptic material at Shreveport Charity Hospital. The patients come in great part from the surrounding countryside, and we, therefore, have little opportunity to observe their subsequent status. They are invariably without prenatal care and their previous vascular history is not often available. However, from returning patients, the few followed in the city welfare clinics, private cases, and frequent conferences with the pathologist and medical staff, we have formulated some ideas about the immediate and remote welfare of the eclamptic mother and her fetus.

The immediate mortality of the mother is augmented by her age, the degree and duration of hypertension, delay in time of treatment after the onset of the disease, the number of fits, pre-existing vascular or renal damage, and oversedation. We feel that we have sacrificed some cases in the past by rigid adherence to a nonoperative policy and have recently adopted the policy of cesarean delivery in fulminating cases, and in patients who become worse after twenty-four to forty-eight hours of medical treatment, especially if a tedious labor is in prospect.

The fetal mortality is increased by the same factors that augment maternal mortality plus prematurity and the lapse of more than forty-eight hours from the time of the onset of the eclampsia to the delivery.

As for the latent effects of eclampsia, a few will be found to have subsequent hypertension because of the pre-existence of pyelonephritis, polycystic kidneys, and glomerulonephritis. A larger number will have had pre-existing essential hypertension.

As for the hypertensive states acquired during the pregnancy, we recognize that they conform roughly to two types, one slowly progressive with little edema, little albuminuria and few symptoms, the other with rapidly mounting pressure, water retention, early symptoms, and a very labile blood pressure. Eclampsia is more common in the latter group, but the former not infrequently become suddenly worse and have unpredicted eclampsia. In either group, if the blood pressure was normal before pregnancy, we classify them as pre-eclampsia. They are regarded pathologically and possibly etiologically as eclampsia, though they are not manifestly such.

We feel that there is no reason to re-classify these obstetric diagnoses because of persistence of hypertension after the pregnancy. It is our opinion that both groups are made up of women who by heritage have the nervous, endocrine, and vascular background that makes them subject to development of vascular or vascular-renal disease. Without delving precariously into the etiology of pre-eclampsia, we surmise that pregnancy toxemia results from the liberation of angiotoxic or angiotonic materials by the kidney, placenta, or both, or, that pregnancy depresses the organism's ability to inactivate these materials. In any event, the development of toxemia is enhanced by pre-existing vasolability or latent hypertension.

The persistence of hypertension after all toxemias of pregnancy is at the rate of 40 or 50 per cent and after those having eclamptic convulsions is probably 15 or 20 per cent. In either of the above groups, the persistence of hypertension is determined by the pre-eclamptic course and not by the eclamptic outbreak itself. There are many factors in the prenatal course that predetermine the ultimate vascular status, such as age at the eclamptic attack and age at follow-up periods, complicating pyelonephritis, family history of hypertensive disease, etc., but the two most important factors seem to be the duration and height of the pre-existing blood pressure and the added assault of a subsequent toxemia. The added hypertension after the second toxemia is unrelated to the occurrence of convulsions and is in proportion to the duration and intensity of the toxemia and to the immeasurable underlying vascular lability.

I infer that the 32 pregnancies among the 9 patients having subsequent pregnancies in Dr. McClellan's series were not among those available for follow-up study, and that he does not know whether or not they had nonconvulsive hypertension with the succeeding pregnancy or hypertension after their subsequent pregnancies. Chesley and Somers' recent survey of the sequelae of eclamptic women at the Margaret Hague Maternity shows a relatively increased incidence of hypertension over Wetherby's and Saller's groups similar to that shown by Dr. McClellan's cases over the Wilson County control groups.

All in all, we feel that the future medical welfare of patients who have had eclampsia is not bad provided it was not preceded by prolonged hypertension, but that future pregnancy is fraught with danger of recurrence of toxemia that will result in permanent hypertension unless it is brought under prompt control by medical management or termination of the second toxic pregnancy. If the recurrent toxemia is severe or long standing, we perform puerperal sterilization on the patient. If the previous course is unknown and the present blood pressure is not severely elevated, the heart not enlarged, the urine well concentrated, the eye grounds relatively normal, we have her return at three months for further study. We see no reason to subject any hypertensive woman who already has two or three babies to the hazardous test of future pregnancy, notwithstanding the exceptional case that stands recurrent toxemia well.

Dr. McClellan's contribution indicates that the subsequent welfare of the eclamptic woman is not as bad as some of us had thought, but I do not think he intends to convey the idea that we are yet in a position to assume a cavalier attitude toward the future cardiovascular renal welfare of the eclamptic woman.

DR. R. E. ARNELL, NEW ORLEANS, LA.—Among the 24,205 obstetric admissions to the New Orleans Charity Hospital during the five-year period ending Jan. 1, 1941, there were 220 cases of eclampsia, an incidence of 0.90 per cent. In 4 of the patients with eclampsia, convulsions had been present in a previous pregnancy, a recurrence incidence of 1.8 per cent. From these gross statistics it would appear that a patient with a history of eclampsia is twice as likely to have eclampsia in a subsequent pregnancy as one whose obstetric history is normal.

In an attempt to determine the late effects of eclampsia and to evaluate the medical and obstetric future of these cases, 30 patients with a history of eclampsia, one to five years previously, were admitted to the hospital for study. Numerous examinations and tests were made in each instance, including complete physical examination, urinalysis, urea clearance, blood chemistry, vasomotor lability, eye grounds, electrocardiogram, and liver function. Except in one case all were normal. This patient exhibited an elevated blood pressure and apparently had an essential hypertension.

We are in agreement with the essayist that demonstrable cardiovascular renal effects following eclampsia are relatively rare. Furthermore, if they do occur, the patient may have had an encephalopathy due to hypertensive or renal disease as the basis for the convulsions rather than a specific eclampsia. We are of the opinion that this occurs not infrequently.

DR. E. L. KING, NEW ORLEANS, LA.—I believe we might estimate the amount of damage that has been done by the eclampsia if we could get a history of that patient for two or three years before the pregnancy that would tell whether there is any underlying factor that might induce the eclampsia. It is evident that pure 100 per cent eclampsia developing in a healthy patient very seldom leaves a permanent lesion.

Another question in this connection is what are we to tell patients regarding future pregnancy. I have known instances where patients who had eclampsia

have been warned never again to become pregnant. This is unnecessary, and keeps the patient in a state of worry for fear of possible pregnancy. I think, however, we should warn these patients not to become pregnant too soon, for it takes a long time to get over the damage.

I have one patient, treated a good many years ago in her first eclamptic attack, whom we warned to wait reasonable time before becoming pregnant again. She disregarded the warning and inside of four months she was again pregnant. She developed a mild attack of eclampsia within the year. After that she listened to reason and waited four or five years, and went through her third pregnancy successfully, and then after four or five years went through another. She has a hypertension of 240 to 245 systolic at present, so that she does have damage as the result of two attacks of eclampsia.

DR. GEORGE KAMPERMAN, DETROIT, MICH.—We use the term eclampsia rather loosely. In a discussion like this we should not speak of eclampsia as being synonymous with toxemia, but rather we should consider eclampsia as being a specific type of toxemia, the chief characteristic of which is that it is a condition which does not exist prior to the particular pregnancy but develops during the pregnancy. The question is whether such a condition is likely to have late cardiovascular and renal sequelae. Of course it is reasonable to expect that other types of toxemia which antedate the pregnancy should persist after the pregnancy is terminated.

In the early Williams' textbooks, the opinion was expressed that an attack of eclampsia might cause an immunity. It seems to me that this earlier view is definitely challenged by the work of Peckham who found that a surprising number of eclamptic patients later on showed evidences of renal disease. My belief is that eclampsia is not as innocuous as far as late sequelae are concerned as we formerly thought it was.

DR. MCCLELLAN (closing).—The statements of the patients who were contacted by letter are the only source of information we have regarding their condition. Their specific reference to the absence of recurrence of convulsions can be relied on, I am sure. This fact, along with our observations of patients seen in pregnancies subsequent to the one in which eclampsia occurred, I believe, makes the statement regarding recurrence of eclampsia reliable.

I quite agree that one should not tell these patients that they should never become pregnant again or that it will be all right to conceive again. They should be followed for a year with frequent blood pressure readings and urinalyses and then advised either against pregnancy or that they might again become pregnant in two or three years.

I would like to emphasize again the importance of differentiating hypertensive vascular disease, vascular nephritis, and glomerulonephritis. Reference was made to Peckham's series in which a certain percentage of post-eclamptics had chronic nephritis. The above differentiation was not made, and unless it is, the figures reported are misleading.

DIAPHRAGMATIC HERNIA IN THE NEWBORN INFANT*

JOHN A. HAUGEN, M.D., AND C. J. EHRENBERG, M.D.,
MINNEAPOLIS, MINN.
(From the Department of Obstetrics and Gynecology, University of Minnesota)

INTERFERENCE with the establishment of normal respiration in the newborn should evoke the interest of the obstetrician, even though the ultimate responsibility for care and treatment may properly belong in other divisions of medical practice. All entities causing newborn respiratory embarrassment are, therefore, obstetric problems.

Respiratory difficulties of central nervous system origin, such as from intracranial hemorrhage and from obstetric analgesics and anesthetics, have received much attention. Recently our attention has been called to respiratory difficulties which result from abnormalities in the chest cavities themselves. An example of this is the report, in 1939, by DeCosta describing and reviewing spontaneous pneumothorax in the newborn, emphasizing that early recognition and immediate treatment will save many of the infants so affected.

The recent occurrence of two cases of congenital diaphragmatic hernia in the newborn infant, precipitated a review of the subject. This condition was formerly considered to be extremely rare and until 1935 was thought to be unamenable to treatment. It is in reality not rare, and, furthermore, can be treated surgically with more than a 60 per cent recovery.

CASE 1.—The infant was a 3,400 gram female born at term after a labor of four and one-half hours. The mother was a primigravida, aged 28 years. There was no history of congenital defect in either parent. The infant breathed spontaneously and cried lustily. She was taken to breast five times the following day and nursed well each time. The baby's progress continued uneventfully until her fourth day of life, when, after a breast feeding, she became cyanotic. This lasted but a few minutes. Following the next feeding the cyanosis became so severe that oxygen was administered. The attending resident pediatrist reported the attack to be so severe that he thought the infant would die. Upright position and oxygen were continued. Examination showed that the heart was pushed to the right and no breath sounds were heard in the left chest. An x-ray revealed a left diaphragmatic hernia. On the ninth day, a laparotomy was performed. The entire small intestine and the spleen were in the left chest cavity. These viscera were replaced in the abdomen and the defect closed. She made an uneventful recovery and was discharged on the twenty-ninth day of life, twenty days postoperatively. The infant's development has continued normally.

*Read at the Thirteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, New Orleans, La., October 2 to 4, 1941.

CASE 2.—A full-term male infant, weighing 2,800 Gm., was delivered by low forceps after rotation of the occiput from a posterior position to the anterior. Labor lasted but four hours. The mother was a

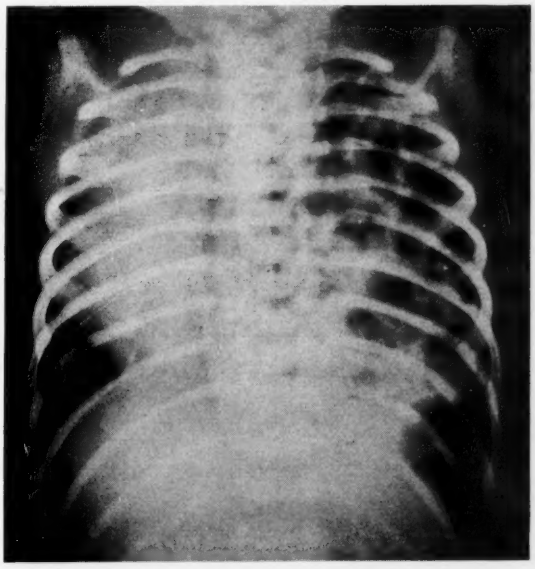

Fig. 1.—Case 1. X-ray film, taken preoperatively, showing left diaphragmatic hernia with intestinal tract in the left chest cavity, and the mediastinum displaced to right.

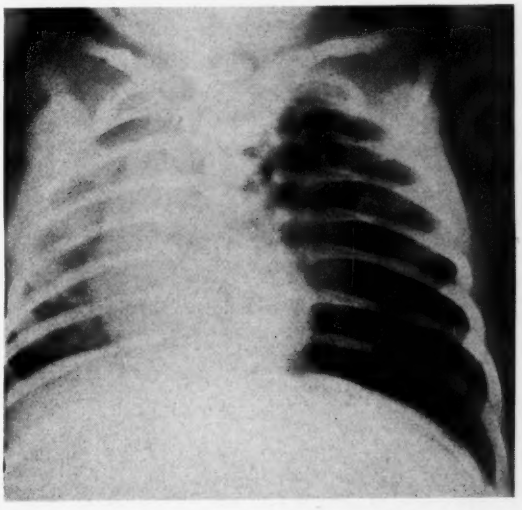

Fig. 2.—Case 1. Eleven days postoperative, showing diaphragm intact, mediastinum returning to center, and with the left lung partially expanded.

29-year-old primigravida. Both mother and father had a negative history for congenital defects. The child gave a single weak cry which was followed by cyanosis and labored grunting respirations. The larynx was visualized with a directoscope and the air passage proved to be clear. Oxygen was administered, which relieved the cyanosis somewhat.

Breath sounds were absent in the right chest and the mediastinum was found to be displaced to the left. An x-ray revealed a diaphragmatic hernia on the right side. The infant's condition became progressively

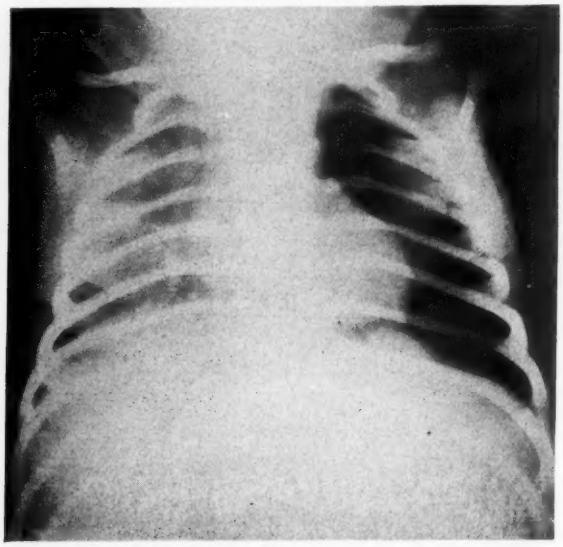

Fig. 3.—Case 1. Fifteenth postoperative day, showing further expansion of the left lung.

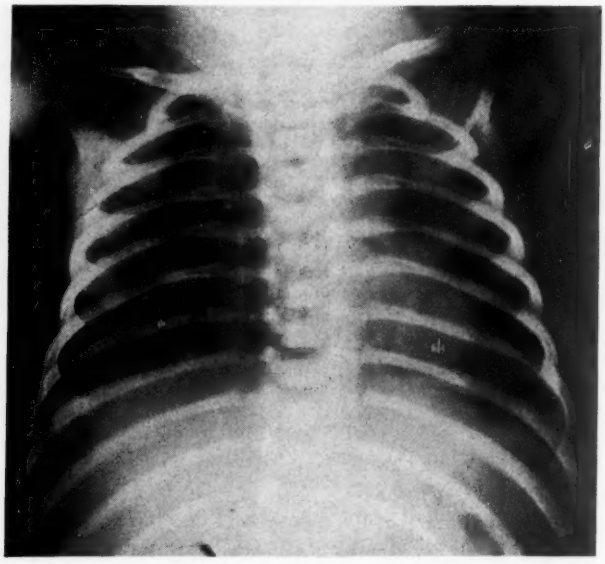

Fig. 4.—Case 1. One month postoperative. Complete cure.

worse. Approximately six hours after birth, the abdomen was opened through a right rectus incision. Nearly the entire gastrointestinal tract and about half of the liver was in the right chest cavity. These viscera

were replaced in the abdomen and the large defect was closed with interrupted chromic catgut sutures. The child died while the abdominal wall was being closed.

A review of the literature reveals a distinct change in thought regarding the incidence and surgical treatment of this condition.

Vannesson, in 1912, reported 34 cases in the newborn, all discovered at autopsy. He stated that the prognosis was grave and that no treatment had been devised.

In 1914, Broca described the condition accurately. He stated that nearly all cases were discovered at autopsy, and he gave the operative mortality as 90 per cent.

In Abt's text on *Pediatrics*, Richter made the statement that congenital large hernias, present from birth, offer little opportunity for surgical treatment.

In 1934, Tremolieres stated that the large congenital diaphragmatic hernias are not amenable to surgical treatment.

Griffith and Mitchell, in 1927, devoted but two paragraphs to the subject with the conclusion that the condition is rare. They stated that surgery is indicated only when obstruction occurs and that it is not likely to be of any avail.

Woolsey, in 1927, was one of the earlier writers to express a change in viewpoint. He collected 106 cases from the literature. In his entire group there was a 71 per cent mortality. It is of interest that he stated that had an early diagnosis been made and operation performed, this figure might have been markedly reduced.

Truesdale, in 1935, collected 303 cases in infants and children. Forty-four had been operated upon, 24 successfully and 20 with fatal termination, a mortality rate of 45.5 per cent. This is quite a different result than was described by the earlier writers.

Truesdale's own series of congenital diaphragmatic hernias totaled 10 cases, all of which he operated upon with but one death. One patient was operated upon three times for recurrences, so his operative mortality was only 7.7 per cent.

Truesdale strongly advocated that operation should be done in the early weeks or months of life.

Wyatt recently reported three patients operated upon in the immediate neonatal period, two of whom survived. His conclusion was that if we expect to reduce the mortality of congenital diaphragmatic hernia, the infants must be operated upon in the first hours or days of life.

INCIDENCE

In a series of 5,269 autopsies on stillbirths and infants up to one year of age, from the Department of Pathology at the University of Minnesota, there were 38 diaphragmatic hernias, or one in 139 autopsies in this age group.

The Chicago Lying-in Hospital has a series of 1,700 infants and fetuses born with malformations. Potter states that there were 70 diaphragmatic hernias in this group. It is of interest that 53 of these infants were liveborn and 17 stillborn. Ten of these 70 infants were

born at Lying-in Hospital. These ten were from a period covering 21,000 deliveries. During most of the years of this period about 95 per cent of the dead babies were autopsied. Consequently, one might assume that these ten are practically all that occurred among infants born at Lying-in Hospital during this time.

These two series indicate that this condition should not be considered a medical oddity.

Diagnosis.—The obstetrician's main concern is with symptoms and signs that occur immediately or in the first few hours after birth. Final diagnosis can be made with ease by x-ray. However, certain signs and symptoms are frequently present which make a clinical diagnosis possible. There is no interference with the mechanism with initiates respiratory attempts; consequently, these babies, in the absence of other abnormalities, will make their initial respiratory attempts normally and promptly. A characteristic single weak cry followed by cyanosis is described by Greenwald and Steiner. This is followed by convulsive attempts at respiration, bringing into play all of the auxiliary muscles. Displacement of the mediastinum away from the affected side with change in percussion note and absence of breath sounds is the rule. Occasionally, gurgling sounds can be asucultated over the thorax due to the presence of intestines in the chest cavity. Our second case presented this entire picture.

Other newborn infants appear normal until they attempt to nurse. This procedure usually precipitates respiratory embarrassment with cyanosis. Our first infant nursed apparently without difficulty for a few times. However, on the fourth day, after obtaining some milk by nursing, it became markedly cyanotic.

Whether the condition becomes manifest at the original respiratory efforts or whether it follows ingestion of food, cyanosis and grunting labored respirations appear. Physical examination of the chest will disclose the above signs and the diagnosis can be immediately proved by x-ray.

SUMMARY AND CONCLUSIONS

1. A review of the literature reveals that congenital diaphragmatic hernia, formerly thought to be rare, is actually not rare.

2. Until 1935, treatment was generally considered to be useless. Since that time more than 60 per cent recovery has been reported as a result of adequate surgical interference. Thus early diagnosis and immediate treatment becomes imperative.

3. Two cases of congenital diaphragmatic hernia are reported.

We wish to express our thanks to Dr. O. S. Wyatt, who operated upon both infants, for permission to include his findings in this report.

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DISCUSSION

DR. J. C. LITZENBERG, Minneapolis, Minn.—In the University Hospital Clinic we have had two instances of diaphragmatic hernia. Neither were recognized and both finally were diagnosed only at autopsy. In each case the obstetrician and the chief of the department of pediatrics tried to make a diagnosis.

As I get older I am impressed with the many things that we used to consider undiagnosable and certainly uncontrollable, but which are now detectable by the recently discovered clinical signs, like those described by Drs. Haugen and Ehrenberg. In these two cases which we had, if these facts that they have brought out had been known, we would certainly have suspected diaphragmatic hernia.

DR. PHILIP F. SCHNEIDER, Evanston, Ill.—The conditions described in this paper are encountered sufficiently infrequently so that I should like to include one case which came to my attention twenty years ago at the Evanston Hospital. Although the heart beat was present for some time after delivery, the apex beat was located to the right of the midline and respirations could not be induced. No autopsy was permitted, but x-ray of the chest revealed the left chest cavity completely filled with intestines, and the mediastinum displaced almost to the midline with apparent absence of the entire diaphragm on the left side. The x-ray findings in this particular instance, even though death had occurred, were of considerable significance.

DR. HAUGEN (closing).—The point regarding the frequency of multiple congenital defects is well taken. Fortunately in these two cases there were no other defects present.

PREGNANCY IN THE SYPHILITIC MOTHER

A Study of 935 Pregnancies at the Cook County Hospital*

S. J. Benensohn, M.D., Chicago, Ill.

(From the Department of Obstetrics, Cook County Hospital and the University of Illinois, College of Medicine)

THE bad results for a pregnancy occurring in a syphilitic mother are well known. That these ill effects can be prevented by careful prenatal therapeutic procedures has been established beyond a question of a doubt. It is the purpose of this essay to present the results of therapy in a large series of cases from the Cook County Hospital obstetric department. In 1937 the writer, in collaboration with Dr. Hillis,[1] presented a review of a series of 418 cases, part of which has been incorporated in this study which, together with the 517 cases observed since the first series, create a total of 935 cases.

With the advent of syphilis control programs, congenital syphilis should practically disappear within one or two generations. The acme of antisyphilitic legislation has been attained in Denmark[2] where antisyphilitic legislation has been in effect since 1790. Following World War I in 1919, the number of new cases reported each year in Copenhagen had dropped from 3,000 in 1919 to less than 200 in 1933. Congenital syphilis naturally was proportionately infrequent.

Results of Serologic Reactions

At the Cook County Hospital prenatal clinic, all expectant mothers have had routine blood serologic examinations since 1929. The routine required that a patient with a positive serology reaction have a repeat test. If a weak reaction was noted, a provocative test was performed before therapy was instituted. The results of an earlier study revealed a degree of variation of opinion as to the dependability of the serology reactions in pregnancy.

Nakayama[3] after exhaustive studies in pregnant mothers concluded that the blood serology reaction was of very little value in the diagnosis of syphilis. He was of the opinion that the parturient function creates a change in the reactive substance. Wile and Shaw[4] believed that false positive reactions in pregnancy were negligible. Lawrence[5] investigated the clinical significance of 839 incomplete Wassermann reactions and found clinical symptoms in 70 of 250 cases with weak positive reactions. Spiegler,[6] on examination of 6,580 pregnant women, found that nonspecific reactions (false positive[5]) occur in pregnancy no more fre-

*Presented at the regular meeting of the Chicago Gynecological Society, October 17, 1941.

quently than in the nonpregnant state. During the past five years at the clinic of the Cook County Hospital as much significance has been attached to a weak serologic reaction as to the complete reaction.

Each patient was interviewed carefully for a history suggestive of syphilis and attempts were made to obtain a report on the husband's Wassermann reaction. A previous survey had disclosed that among pregnant patients who had weakly positive reactions and were not treated, 3.5 per cent of these pregnancies resulted in syphilitic complications. This led to a careful search for other evidence of syphilis, such as the husband's Wassermann reaction, history of secondary lesions, previous stillbirths, premature labor and late abortions. When a suggestive history was obtained, therapy was instituted, despite the realization that an occasional patient would be treated unnecessarily.

TABLE I. RESULT OF SEROLOGY TESTS (WASSERMANN AND KAHN)

A Comparison of Reactions During Pregnancy and at Six Weeks Post Partum in 177 Cases

(All new cases without previous therapy)

Series 1.	Reaction weak or negative during pregnancies but strongly positive at 6 weeks post partum, despite therapy	29
Series 2.	Reaction strong in pregnancy but negative or weak post partum	40
Series 3.	Reaction strong during pregnancy and post partum	86
Series 4.	Reaction weak during pregnancy and post partum	22
	Total	177

Table I reveals a survey of the intensity of serologic reactions in 177 cases. All tests were made at the Chicago Board of Health laboratories and included both Wassermann and Kahn reactions. The 177 patients had received no treatment prior to the pregnancy, and received a minimum of five to a maximum of twenty treatments before delivery. The inconsistency of the results as disclosed in Table I corroborates the belief that weak serologic reactions during pregnancy must receive the same degree of importance as the stronger complement fixations.

INCIDENCE

Estimates of the incidence of syphilis among prenatal patients vary. Reports from clinics among the colored in the south have revealed incidences as high as 30 per cent with variations to 3 and 5 per cent in other parts of the country. With an increase in legislative and educa-

TABLE II. INCIDENCE OF SYPHILIS AMONG PRENATAL PATIENTS BASED ON SEROLOGY REACTIONS

YEAR	TOTAL PATIENTS	SYPHILITIC	INCIDENCE
1932-1936	10,016	418	4.17%
1940 to April 1, 1941	3,325	125	3.76%

tional programs, the incidence should gradually decline. The results of such programs have already brought a reduction in the clinic at the Cook County Hospital.

Table II reveals a 9.8 per cent reduction in the incidence after an interval of four years.

This reduction in incidence is all the more striking since many patients are now being referred to the clinic from other agencies for therapy and delivery after the diagnosis has been made.

MODE OF INFECTION

The mechanism by which the fetus becomes infected is not clearly understood since it is possible for a syphilitic mother to give birth to a nonsyphilitic infant. Twenty-three of 50 untreated mothers in this series and 26 of 70 in the previous series gave birth to nonsyphilitic infants. With the advent of the Wassermann reaction, older concepts of the transmission of the infection have been discarded. Profeta's law and Colle's law are no longer tenable.

Cooke[7] presents a logical and plausible explanation which our experience has tended to confirm. Cooke is of the opinion that when the initial infection occurs during pregnancy the extensive spirochetemia occurring during the primary and secondary stages of the disease always infects the placenta and then the fetus. However, since the infection has passed the acute stage in most pregnant mothers, the infant may not be infected. Transmission is dependent upon active spirochetes in the blood stream and, therefore, Cooke believes that transient periods of spirochetemia occur in cases of latent syphilis and that these periods of spirochetemia become less frequent as time passes on. If a period of spirochetemia occurs during pregnancy, then the fetus becomes infected. It is interesting that many syphilitic mothers have never had clinical manifestations of the disease and give no suggestive history. Cooke suggests that such a patient may acquire the infection from her husband long after he has received his initial infection and that the spirochete lies dormant in the testicle and is transmitted to the mother by means of the semen. Entering the mother in a dormant state, the spirochete does not produce the active manifestations of the primary or secondary stage, but remains dormant in some organ in a latent or attenuated state. The chances of transmission from mother to infant have been quoted as from 100 per cent to 50 per cent.

Since it is impossible to predict when a period of spirochetemia will occur during a given pregnancy, the object of therapy should be toward maintaining an adequate amount of germicidal agent in the blood stream at all times throughout the duration of the pregnancy. Patients with longstanding untreated syphilis stand a better chance of giving birth to a nonsyphilitic infant than do patients with a recent syphilis. Also patients who acquire primary lesions during later months of pregnancy may not necessarily have the syphilis transmitted to the fetus, and patients with secondary lesions untreated should have almost 100 per

cent transmission to the pregnancy. Third generation syphilis should be rare, if a possibility at all.

TREATMENT

Following a diagnosis of syphilis, the patient is instructed to report to the antisyphilitic clinic once per week throughout the pregnancy. In addition to the routine prenatal management they are given intensive antisyphilitic therapy consisting of the administration of 0.6 Gm. of neoarsphenamine intravenously and 0.13 Gm. of bismuth salicylate intramuscularly every week until delivery. In selected cases, because of technical difficulties, 0.2 Gm. of bismarsen is administered intramuscularly as a substitute. There are no rest intervals during the prenatal period. This plan of management is carried out with the advice and cooperation of the department of dermatology of the hospital, and in the event reactions occur or there is a question of modifications or variations of treatment, the dermatologists are consulted.

A ward, nursery, and delivery room separate from the remainder of the maternity division are set aside for the delivery of these patients. At the time of delivery or shortly thereafter, all infants are examined for evidence of syphilis. Hinrichsen,[8] in an exhaustive review on the interpretation of modern serology tests, mentions the conclusions of Roby and Lembcke that the cord Wassermann reaction reflects almost exactly the condition of the mother's blood at the time of labor and that the substance causing the positive reaction passes completely out of the child's blood within two months. Since a negative cord blood reaction is valueless in a treated mother and a positive reaction is of no significance as far as the infant is concerned, the practice of routine cord blood reactions had been discontinued many years ago.

All infants and stillbirths are x-rayed for evidence of syphilis of the long bones. Autopsied infants are examined intensively for evidence of syphilis, including microscopic examination of the metaphysis of long bones by the pathology department. If no evidence of syphilis is found, the patient is instructed to return to the clinic with her baby six weeks post partum, at which time blood specimens are obtained from both mother and child for serology reactions. Roentgenograms of the long bones of the infant are taken at the six-week period and are repeated at three months, six months, and one year whenever possible.

If at any time syphilis is suspected or diagnosed, the infant is referred to other agencies for therapy. The mother is offered therapy for one year following delivery. It is noteworthy that 17 per cent of all patients return pregnant again within one to two years. All patients before discharge are urged to resume treatment whenever they become pregnant. The 935 pregnancies occurred in 722 women.

RESULTS OF TREATMENT

The results of therapy are divided into "failures" and "salvaged." The failures include all abortions beyond the fourth month; premature labors of macerated and nonmacerated syphilitic fetuses; all stillbirths and neonatal deaths, and all infants who after delivery present evidence of congenital syphilis. Although not all of the macerated fetuses can be charged to syphilis, nevertheless they are considered as failures because of the maternal syphilis. Salvaged cases include all infants followed for at least six weeks who do not present evidence of congenital syphilis. It is admitted that a few of the salvaged cases may sometime later in life present evidence of syphilis, but the difficulty of follow-up for more than one year limits the recording of such cases.

The statistics reveal that only 39 per cent of all untreated mothers will have the infection transmitted to the fetus. Antisyphilitic therapy during pregnancy, although carrying a failure of 6.7 per cent in the entire group, compares very favorably with 39 per cent of syphilitic pregnancies in the untreated group (Table III). The total salvages in

TABLE III-A. RESULTS OF 517 CASES OF SYPHILIS—TREATED AND UNTREATED (PRESENT SERIES)

AMOUNT OF TREATMENT	5 OR LESS	6 TO 10	OVER 10	NONE	TOTAL
Live, nonsyphilitic infants	125	103	213	76	517
Failures, including stillbirths, syphilitic infants, abortions	9	9	12	28	58
Percentage salvaged	92.8	91.3	94.4	63.2	
Results of 418 Cases—Previous Series					
Live, nonsyphilitic infants	106	105	137	70	418
Failures, including stillbirths, syphilitic infants, abortions	12	9	3	30	54
Percentage salvaged	88.7	91.5	97.9	57.2	

TABLE III-B. SUMMARY TOTAL CASES—BOTH SERIES

Treated cases	789
Failures	54
Percentage salvaged	93.3%
Untreated cases	146
Failures (syphilitic pregnancies)	58
Percentage	61.0%

both series are remarkably consistent. The results achieved among the patients receiving more than ten treatments are especially noteworthy. There were 15 failures in 350 cases. This will be given further consideration.

Table IV demonstrates the efficiency of intensive therapy, particularly when the parturient individual receives more than ten treatments during pregnancy. Better results are to be expected in those patients given even a minimum amount of treatment than among the untreated patients. A comparison of both series of cases reveals conclusively that in

TABLE IV. A COMPARISON OF RESULTS AMONG 608 NEW CASES PREVIOUSLY UNTREATED AND 327 OLD CASES PREVIOUSLY TREATED

	New 354				*Old 163*			
NUMBER OF TREATMENTS	1-5	6-10	10 OR MORE	NONE	1-5	6-10	10 OR MORE	NONE
	New Series							
Number of cases	86	71	147	50	39	32	66	26
Failures	6	6	11	23	3	3	1	5
Per cent salvaged	93.1	91.6	92.6	54.0	92.6	90.7	98.5	82.0
	New 254				*Old 164*			
NUMBER OF TREATMENTS	1-5	6-10	10 OR MORE	NONE	1-5	6-10	10 OR MORE	NONE
	Old Series							
Number of cases	63	61	90	40	43	44	47	30
Failures	8	3	3	20	4	5	0	10
Per cent salvaged	87.2	95.1	96.7	50.0	90.7	88.7	100	66.0

patients receiving adequate therapy, particularly in patients who have received treatment before pregnancy, congenital syphilis can be completely prevented.

In order to analyze the results of therapy, the failures were classified as to termination in the recent series of 517 cases.

TABLE V. SUMMARY OF FAILURES (517 CASES IN RECENT SERIES)

	ABORTIONS (4 months)	STILLBIRTHS	NEONATAL DEATHS	BORN ALIVE WITH SYPHILIS
Untreated 76 patients	8	10	7	3
New patients treated (354)	5	9	3	2
Old patients treated (163)	6	5	0	0

All syphilitic mothers whose pregnancies terminated beyond four and one-half months of uterine gestation in macerated fetuses in the absence of other maternal complications were considered as syphilitic. An average of two treatments was given the 11 mothers whose pregnancies terminated in abortion. In the 9 new cases in the stillbirth group, 3 mothers received more than 10 treatments, but in the older patients treated only 1 of 6 received adequate therapy. In the group of 3 neonatal deaths, 1 infant weighed 2 pounds 10 ounces, the mother receiving only 3 treatments; the other 2 infants were over 5 pounds and in one instance the mother received 10 treatments. In all cases a positive diagnosis of congenital syphilis was made either pathologically, serologically or roentgenologically.

In 4 of the failures the mothers received bismarsen intramuscularly because of technical difficulties in giving intravenous therapy. One of these patients received approximately 30 injections and, although born alive, the infant had syphilis. In the other three cases, one patient received 3, another 8, and the third 7 bismarsen injections. All of these

pregnancies terminated in stillbirths. Only 30 patients received bismarsen during pregnancy and 4 failures are recorded. These cases are included in the tables presented and demonstrate the importance of intravenous therapy.

FOLLOW-UP AND THE DIAGNOSIS OF CONGENITAL SYPHILIS

As stated previously, an attempt is made to follow infants for at least one year. However, since the second series of cases was begun, additional social agencies have been available for follow-up, and thus it was possible to learn of nearly every case of congenital syphilis among the babies delivered whose mothers failed to return them for follow-up. At the present writing 95 per cent of all infants delivered during the past year are returning to the clinic for periodic check-up.

A positive serology reaction beyond the eighth week of life establishes the diagnosis of congenital syphilis beyond a question of doubt.

Roentgenologically the earliest characteristic lesion seen is a syphilitic osteochondritis (a definitely widened epiphyseal margin and a rarefied submetaphyseal zone). It is this finding that has caused much confusion in the diagnosis of early congenital syphilis. Dr. Philip Aries[9] of the pediatric department, after a study of 300 roentgenograms taken of infants born of syphilitic mothers at the Cook County Hospital, has helped clarify the value of roentgenologic manifestations in the diagnosis of early congenital syphilis and believes that a positive diagnosis must be made with extreme caution.

With the results of therapy as shown in this paper and as reported from numerous other clinics, in the absence of positive serology in the infant, the attending physician should not rely in toto on x-ray findings and early serology reactions, but should seriously consider the amount of therapy given the mother during pregnancy before making a diagnosis of congenital syphilis.

THIRD-GENERATION SYPHILIS

Cases have occasionally appeared in the literature of third-generation syphilis. Twenty cases of known congenital syphilis were followed in the clinic and delivered in the hospital. Eighteen patients had received therapy for various periods before pregnancy. Sixteen patients received adequate treatment during the present pregnancy, and 4 received inadequate treatment. However, one case is of special interest.

The patient, A. J., aged 18 years, colored, married one year, had no previous serology tests and was seen for the first time in the fifth month of pregnancy. She had the typical Hutchinson's teeth and the Kahn and Wassermann reactions were 4+ positive. The mother of this patient was interviewed and it was learned that she had been married twice. The patient was the child of her first marriage. Five years after the birth of this child she was told she had syphilis and was treated for five months. Her first husband had also been taking "shots." Her second

husband had a negative Wassermann reaction. The patient was not treated during this pregnancy and gave birth to a seven-pound female which to the present time has been serologically and roentgenologically negative. It would have been surprising if the infant had had syphilis.

FIVE-DAY INTENSIVE THERAPY

The incidence of tragedies for the pregnancy among patients who have secondary lesions during pregnancy is extremely high. In 9 such patients, there were 5 failures; 2 abortions, 2 macerated stillbirths, and 1 infant congenitally syphilitic. Only 2 of the 5 failures received adequate therapy. The thought that these failures could be prevented by massive dose arsenotherapy over a five-day period seemed worthy of trial. With the cooperation of the dermatology department, under the direction of Dr. H. Rattner, 8 patients have been treated by this technique (2 with primary lesions and 6 with secondary lesions).

The first patient with a primary lesion near the fourchette was admitted to the hospital at term; continuous therapy was administered at once and after forty-eight hours of therapy the patient delivered a live, nonsyphilitic infant. The mother received 480 mg. of mapharsen (240 mg. of arsenic) before delivery. The infant showed no deleterious effects and chemical analysis of the infant's blood on the fifth day of life revealed 0.0005 mg. of arsenic per cubic centimeter of blood specimen. The blood chemistry of the mother revealed 0.0006 mg. per cubic centimeter of blood specimen. A second patient, one with secondary syphilis, eight months pregnant, was given five days of intensive therapy (1200 mg. of mapharsen). She returned one month later and delivered a seven-pound nonsyphilitic infant. This baby at two and a half months is still negative. The mother is showing evidence of becoming seronegative. Shortly after delivery the blood of the mother revealed 20 Kahn units; the baby's blood was negative.

Two additional patients have delivered nonsyphilitic infants. One patient aborted in the third month of uterine gestation several days after completing therapy, and the remaining three are still undelivered. One of these undelivered patients had a primary lesion and was treated during the second month of pregnancy.

In these 8 patients treated intensively, 5 have revealed serologic improvement and 3 complete reversal. This small series of cases suggests that this new method of attack in properly selected cases may be harmless to the fetus and yet offer promise for therapy in the acute stage of syphilis during pregnancy. This method of treatment requires further investigation to evaluate properly the fetal results and the danger to the mother. Great caution must be exercised in treating these mothers and therapy must be stopped at the slightest evidence of reaction.

REACTIONS

During the earlier series of 416 cases, there was one maternal death due to an arsenical exfoliative dermatitis. In the present series of 517 cases there were no deaths associated with therapy. Greater care has

been exercised in deferring treatment in patients who develop dermatosis of the slightest degree, albuminuria, elevated blood pressure or temperature. Severe reactions are infrequent. Nausea and vomiting two to four hours following the injection seem to be most frequent. No nitritoid crises or cases of yellow atrophy have been observed. Occasionally a mild syncope has been noted, but this has usually been on a psychic basis. Opinion differs in the literature as to the prevalence of reactions.

Cole,[10] in presenting the results of the Cooperative Clinical Group studies, concludes: "The pregnant syphilitic woman is a good risk for arsenical therapy," after analyzing the reaction incidence in 4,600 injections given to 603 expectant mothers at five university clinics. Stokes,[11] however, is of the opinion that the pregnant woman is not a suitable candidate for strenuous treatment regimens and that any sign of reactivity should be taken more seriously than in the normal cases. Ingraham,[12] comparing the reaction incidence among cases at the Philadelphia General Hospital with those of the Cooperative Clinical Group, finds a much higher incidence of reactions; "in pregnant women, nausea, vomiting and diarrhea are three and a half times more frequent than in the nonpregnant; jaundice two times more frequent and evidence of kidney strain sixteen times." He presents seven deaths in pregnant patients receiving arsenic therapy and analyzes 35 additional cases in the literature, two-thirds of whom died of acute encephalopathies. Plass and Woods[13] reported three fatalities due to arsenical hemorrhagic encephalitis and conclude that the pregnancy makes the syphilitic patient more susceptible to the deleterious effect of arsenic. Paley and Pleshette[14] report a single case of hemorrhagic encephalitis in 1,200 treated prenatal patients at the Harlem Hospital; they found 158 cases of hemorrhagic encephalitis following arsenic therapy reported in the literature. They suggest using small doses initially and stopping therapy when headache, dizziness, or generalized pains begin. Since capillary hemorrhage is the essential pathology in hemorrhagic encephalitis, they suggest the administration of vitamin K and calcium during the period of therapy.

It is noteworthy that in all the cases reported as having developed encephalopathies, the initial reaction occurred shortly after the first, second, or third injection. In view of the number of cases reported we have been most fortunate in having experienced none of these complications. The only possible explanation for this lack of serious complications in our patients is that therapy is stopped without hesitation in the presence of a temperature of 99.2° F., a trace of albumin in the urine, elevation of blood pressure readings to 140/90, the presence of mild upper respiratory or other infections, the slightest pruritus, local or generalized, and finally if the patient reports severe or persistent vomiting after any single injection. The results we have obtained tend to confirm the contention that the pregnant syphilitic tolerates arsenotherapy as well as the nonpregnant patient.

CONCLUSIONS

1. The results in a total series of 935 pregnancies occurring in syphilitic mothers are presented; 789 of these patients received therapy with a 93.3 per cent salvage; 146 mothers were untreated and only 61 per cent gave birth to apparently nonsyphilitic infants.

2. Among 350 patients who received adequate therapy, all but 15 pregnancies terminated satisfactorily.

3. Patients receiving therapy both prior to and during pregnancy have almost a 100 per cent chance of having a nonsyphilitic infant.

4. All patients with a history of syphilis should be treated during each pregnancy without consideration of serologic reactions or amount of previous therapy.

5. Serologic reactions during pregnancy present a degree of inconsistency. When weak reactions are repeatedly observed, therapy should be instituted, especially if a history is obtained of stillbirth or late abortion, suspicious lesions, or a positive reaction in the husband.

6. Germicidal agents to be effective must be administered intravenously.

7. Third generation syphilis is an extremely rare condition.

8. Intensive therapy during pregnancy requires additional investigation, but from the little experience presented apparently is a harmless procedure in properly selected cases and offers an excellent prospectus for the pregnancy in a patient acquiring a primary lesion or developing secondary lesions during pregnancy.

9. In the absence of positive serology reactions in the newborn, consideration should be taken of the amount of treatment given the mother during pregnancy in making a diagnosis of congenital syphilis.

10. The dangers of arsenic therapy for the mother must always be considered, and therapy should be stopped at the slightest indication that a reaction may be imminent.

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185 North Wabash Avenue

DISCUSSION

DR. PHILIP L. ARIES.—The syphilitic pregnant woman who has not been treated adequately during her pregnancy may give birth to a baby that appears normal, or to one that has clinical manifestations of hereditary syphilis during the neonatal period. The latter condition makes the prognosis for life poor, for the infant rarely survives the first weeks or months of life in spite of careful antisyphilitic management. The normal-appearing newborn, if infected with the spirochete, may present no clinical or serologic evidence of syphilis until the fourth to eighth week of life, and in a few instances not until much later. Obviously, it is desirable to institute specific therapy in these infants prior to the development of clinical manifestations, but unfortunately it is often difficult to make a definite diagnosis. The serologic diagnosis, the search for placental pathology, examination of the umbilical vein scrapings for spirochetes, and roentgen ray examination of the long bones for evidence of syphilitic osteochondritis all have their limitations. A careful follow-up period of observation for six months to a year is essential before the ultimate conclusion, that a child is free from hereditary syphilis, can be reached.

A positive Wassermann reaction in the early weeks of life may result from antibodies transmitted from the mother. A positive reaction which becomes less positive, then negative, by the eighth week of life may be found in the noninfected child. Positive evidence of osteochondritis as revealed by the roentgen ray examination of the bones of the newborn is the most reliable criterion upon which the diagnosis of hereditary syphilis can be made. Experience in reading films, however, is essential, otherwise changes from the usual but still within normal limits may be called positive. On the other hand, negative or suggestive findings in the roentgenograms may become definitely positive when the bone is re-rayed after the child has reached the eighth week of life.

After observing the patients for several years, we can accept Dr. Benensohn's conclusion that a syphilitic mother, adequately treated during pregnancy, that is weekly from the fifth month and through the last trimester, has practically a 100 per cent chance of giving birth to an infant free from inherited syphilis.

DR. HERBERT RATTNER.—During the past year in the department of dermatology at the Cook County Hospital, we have treated 270 patients with early syphilis by means of the five-day massive dose technique. About one-third of them have been women ranging in age from 16 to 49 years. We administer to each patient daily, regardless of age, sex, or weight, 0.24 Gm. of mapharsen dissolved in 2,000 c.c. of 5 per cent glucose solution. In five days a patient receives 1.2 Gm. of mapharsen. In our case the solution is administered in a vein of the hand and allowed to flow at the rate of about 40 to 50 drops per minute. No special preparation of the patient is necessary, but we have been careful to select only healthy persons. The experience is perhaps none too pleasant for many of the patients, but it is not a great hardship. Most of them suffer from headache, nausea, vomiting, fever, and pain in the arm for the first day at least, but in general the reactions are minor ones. In three instances, however, we have encountered alarming reactions. There were two cases of toxic encephalopathy and one patient in whom there developed acute glomerulonephritis, hepatitis, ileus, and pericarditis. There have been no fatalities in our group.

The results so far as can be judged this early have been satisfactory. The best results were obtained in the patients who reported for treatment very early. In those with seronegative chancres, the "cures" were apparently 100 per cent. In those with late secondary eruptions the incidence of cure has dropped to about 87 per cent. We have retreated 12 patients either because of reinfection (2 undoubted cases), relapse or superinfection without any harmful effects. Among our patients

there were 10 pregnant women with early syphilis, 5 of whom have delivered apparently healthy infants, the oldest now eight months of age. The other women are awaiting delivery.

In the past few weeks, with the cooperation of Dr. Benensohn, we have undertaken to treat pregnant women with untreated latent syphilis. The same dosage has been used, regardless of the stage of pregnancy. One of our women, as Dr. Benensohn related, was at term when she reported with a chancre. Others were in the second, third, fifth, seventh, and eighth months of pregnancy.

The method of treatment, of course, is a radical departure from the standard methods now in use. The results of the first cases treated in New York in 1933 have been excellent. This has encouraged us because our early results are running a curve that parallels that of the results of the New York group. Were it not for the cases of encephalitis that have occurred (one in about every 200 cases), the method of treatment would be generally adopted. For the present it must still be considered as in the experimental stage until more cases have been treated for a sufficiently long time to allow statistics to tell the complete story.

DR. RICHARD FRANK.—I would like to present a few figures from the syphilitic patients at the Chicago Maternity Center during the last two years. For reasons of comparison I would like to show that the incidence of syphilis in women in Chicago was 2.1 per cent in white women and 14.9 per cent in colored women among a group of approximately 14,000 women examined during 1939. In the two-year period from July, 1939, to June, 1941, 3,051 white women were delivered at the Chicago Maternity Center, with an incidence of 1.6 per cent syphilis (48 patients) and 1,802 colored patients with an incidence of 5.3 per cent syphilis (95 patients).

As to the amount of treatment during pregnancy: Each patient received an average of 11.4 arsenical injections and 17.4 injections of bismuth. That includes those who were put under treatment during the first month of pregnancy as well as those who came in during the last few weeks of pregnancy and had only three or four injections before delivery. Actually 63.7 per cent of all patients received treatment before the fifth month. Each one received an average of 14.2 arsenical injections and 23.7 bismuth injections.

I would just like to bring out one point that Dr. Benensohn did not stress—the importance of early treatment in pregnancy. The treatment must begin before the fourth month. It must go on with strict regularity on a weekly schedule if good results are to be obtained.

Dr. Benensohn mentioned the theoretical presence of spirochetemia all through pregnancy. We do not know if, when and where this occurs, but the only way we might fight it is by maintaining continuously a certain level of a spirocheticidal arsenical in the patient's serum, in order to protect the baby.

As to the results of syphilis treatment in pregnancy: Of 142 patients delivered, 124 have been followed from three to twenty-seven months, and 86.7 per cent have shown no signs of syphilis up to the present time. There was no syphilitic stillbirth, the 9 fetal deaths (early and late pregnancy and neonatal) being due to obstetric complications. Autopsy in these cases did not reveal any syphilitic changes. There was one baby with syphilis of a mother who received only 4 injections and was treated for only three weeks. Six and three-tenths per cent of the babies were not followed up because they could not be located.

DR. I. M. LEVIN.—The excellence of prenatal care at the Cook County Hospital has markedly reduced the incidence of congenital syphilis on the obstetric service. This has resulted in a paucity of material for the venereal service of the Children's Hospital in which we have pioneered with intensive massive intravenous arsenotherapy, the so-called "five-day treatment."

The work of Synder and Speert in 1938 in demonstrating that arsenic is deposited in the placenta of rabbits at the period of viability has many implications. No arsenic is found in the fetus prior to this time, and the concentration in the placenta exceeds by many times that in the fetus. The logic of arsenotherapy after the fourth month of pregnancy is self-evident.

Certain features of serologic reaction in mother and child are commonly overlooked. The mother may give a positive Kolmer and the infant a negative, and vice versa. In neither instance is syphilis ruled out. Serologic negativity on the part of the mother does not preclude syphilis in the child. Cord blood serology is that of the mother at the time of delivery and is not conclusive for the infant.

Quantitative serology is a distinct advance in our diagnostic field. A Kahn titer of higher unity value in the infant than in the mother is almost conclusive evidence of congenital syphilis. Where the child's titer is lower than that of the mother this may be a transmitted serologic reaction, which may disappear within four to eight weeks and the child be free of syphilis. On the other hand after a period of negativity it may again begin to rise, evidence of spirochetal activity and active infection.

It is not easy to make a diagnosis of congenital syphilis. There may be no clinical physical signs. Prior to the work of Caffey and Aries, we thought we could employ bone x-rays as presumptive evidence of syphilis in a very high percentage of infants. We now know that nutritional disturbances, rickets, scurvy, and a variety of disorders may simulate syphilis. Only a positive Wimberger sign (symmetrical osteomyelitis of the medial upper third of the tibiae) is conclusive.

Insufficient attention is given to gross and microscopic examinations of the placenta and cord for evidence of syphilis. Such studies in addition to roentgenographic and serologic examinations should yield the highest percentage of positive diagnoses. Early affirmative evidence of syphilis will make possible the treatment of congenital syphilis at the earliest possible time when massive intravenous arsenotherapy is most effective.

Liston, W. Glen: Trichomonas Vaginalis Infestation, Brit. J. Ven. Dis. 16: 113, 1940.

The author goes into great detail concerning the morphology and species differentiation of the trichomonas parasite. There can be no doubt that the species of trichomonas which are found in man inhabit specifically selected sites.

T. vaginalis has never been found free in nature, and it is a parasite strictly confined to man. It is difficult to know how infection spreads. Carrier cases are numerous, and may be a fruitful source of infection. In persistent cases the cause may be due to the fact that the parasite takes up an abode in and below, rather than on the surface of mucous membranes.

Glycogen in the vaginal epithelium seems to be necessary for the development of the parasite. It is stated that *T. vaginalis* flourishes in the degree of acidity favorable to a Type III vaginal flora, which comprises a great variety of organisms, but small cocco-bacilli predominate.

The author divides the disease into an acute, subacute, and a chronic or a latent form. The symptoms are well known.

The entire principle of treatment lies in eradicating the *T. vaginalis,* restoration of the glycogen to the epithelial cells, and the establishment of Doederlein's bacillus in the vagina. A cure is established when the pH returns to and remains at about 4. The author used carbarsone suppositories exclusively in his routine of treatment.

WILLIAM BERMAN

THE TREATMENT OF HYDROCEPHALUS IN CEPHALIC PRESENTATION

CORNELIUS T. O'CONNOR, M.D., F.A.C.S., AND ARTHUR J. GORMAN, M.D.,
BOSTON, MASS.
(From St. Elizabeth's Hospital, Brighton, Mass.)

THE following case history is deemed worthy of presentation and discussion because it illustrates a new method of treatment in cases of hydrocephalus which we believe is simpler than any previously proposed.

M. O'G., aged 20 years primigravida. Father and mother living and well. Four siblings living and well. She had had no familial diseases or no serious illnesses. Menstruation was normal. Last period occurred on Dec. 8, 1940, and delivery was due Sept. 15, 1941. The patient was seen in consultation by one of the authors (A. G.) on Sept. 8, 1941, with Dr. Joseph MacDonald at St. Elizabeth's Hospital, because of an increase in weight of 13½ pounds during the previous three weeks, an unengaged head, and vague abdominal pains. She was having mild uterine contractions occurring every fifteen minutes. A vertex presented and seemed to be enlarged. The lower uterine segment was rather tense. Fetal heart was in L. U. Q., position and rate was 130. No presenting part could be felt rectally. The cervix was closed and partly taken up. Diagnosis: Pregnancy near term. There was disproportion with a large head, and a question of hydrocephalus. X-ray films revealed a large head above the pelvic brim but the plates were not satisfactory. The patient's pains ceased and she was sent home for observation and re-examination in another week. She re-entered the hospital a week later in mild labor and with a slight bloody show. Rectal examination revealed a cervix 3 cm. dilated and partly taken up, with the membranes bulging through the os. The presenting part, however, could not be felt. The fetal heart was in L. U. Q. position, with a rate of 130. A vaginal examination was done and the membranes were ruptured. The presenting part was then made out to be a vertex which had the consistency of thick, soft, wet leather. Diagnosis: Hydrocephalus. X-ray examination revealed a hydrocephalic head and comparison with the rather unsatisfactory pictures of the week previous demonstrated that a definite increase in the size of the head had occurred during this period. The patient was anesthetized with nitrous oxide and oxygen and light ether anesthesia. The operative field was prepared with tincture of metaphen, sterile drapes were applied and the vagina was flushed with a solution of S. T. 37.* The cervix was exposed with retractors. It was 3 cm. dilated. The child was baptized, using a long glass syringe. A No. 18 gauge spinal puncture needle was easily inserted into the presenting part. Cerebrospinal fluid immediately spurted under pressure. About 1,400 c.c. of fluid were removed. After the initial pressure was released, the rate of flow slowed somewhat. Abdominal pressure on the head resulted in a satisfactory return of the flow through the needle. About twenty-five minutes were spent in allowing the fluid to drain. Labor began almost immediately. X-rays were taken after the tap was finished. It was noted toward the end of the tap, that the head, now greatly collapsed and softened, was rapidly dilating the cervix and coming into the pelvis. Labor lasted one hour. The patient delivered

*Hexylresorcinol solution.

normally. A small episiotomy was done. The child was born alive and lived for two hours. As soon as the child was delivered, intravenous ergotrate, $\frac{1}{320}$ gr., was administered. The placenta separated promptly and was expressed four minutes after delivery of the child. The episiotomy was sutured. The uterus reacted well. The patient's condition was excellent at the end of the delivery. Autopsy of the child revealed marked atelectasis, internal hydrocephalus, spina bifida with meningocele, dorsolumbar atrophy of the spinal cord, and cerebellar adhesions to the dura mater.

DISCUSSION

Current texts do not mention this form of treatment. Irving[1] recommends perforation and version. DeLee,[2] Piper,[3] and Stander[4] recommend the cranioclast if the natural forces are insufficient after perforation. Titus[5] recommends perforation and the cranioclast with slow extraction. Kerr[6] and Montgomery and Bland[7] recommend perforation followed if necessary by forceps application. There is no complete unanimity of opinion because DeLee[2] and Oldfield[8] believe that there is a slight risk of rupture of the uterus if version is attempted. Moreover, Eden and Holland[9] and DeLee[2] believe that the cranioclast is inefficient because it is liable to slip. Practically all writers who go into any detail recommend that perforation be performed either at full dilatation or when the cervix is easily dilatable. It is evident from their statements that a good deal of labor must take place before perforation can be done. Titus[5] further recommends, in Catholic patients, the performance of internal podalic version first and then craniotomy to the aftercoming head when the child is dead. Schumann[10] and Titus[5] insist on the necessity of perforation plus a thorough evacuation of the cranial contents so as to ensure fetal death. Others, such as Jellett and Madill[11] do not insist on the latter.

A consideration of these recommendations makes it obvious that there is unanimity of opinion as to the desirability of perforation so as to ensure two things: (1) A head small enough to be delivered either normally according to some, or by operative means according to others. (2) The desirability of a dead baby, to the extent of direct infanticide in the opinion of some writers. There are, however, rather marked variations in the treatment after perforation and some of the procedures recommended require (1) deep anesthesia, (2) a not inconsiderable amount of training and skill, and (3) a good deal of either vaginal or intrauterine manipulations, or both. Moreover, these latter manipulations take place in a uterus whose lower segment has been subjected to a great deal of stretching both before labor and during labor, a situation not ideal for operative procedures. Again, many of the statements are prefaced by the remark that perforation should be done when the cervix is fully dilated or easily dilatable, a condition not always easy to attain in actual practice. Full dilatation in these cases occurs slowly, the labor often being very inefficient and prolonged. The patient is, therefore, subjected to a good deal of pain which should be obviated if practicable. In addition, the length of labor required for full dilatation can seriously overstretch an already markedly distended lower segment. As far as easy dilatability is concerned, the stretching of the cervix when the lower segment is greatly thinned out is conceivably not without danger. The recommendation of Titus[5] that an internal podalic version should be performed when the patient is a Catholic, provided that the the conditions are such that this is possible without risk to the mother, is, in our

opinion, impractical and dangerous. We do not believe that the proper conditions for version are ever present in these cases. We feel that the great size of the head and the marked thinning of the lower segment contraindicate version in all cases of hydrocephalus because of the great danger of rupture of the uterus. The latter has, in fact, occurred in the practice of one of the authors (C. T. O'C.).

We recommend intraventricular tap and drainage per vaginam with a spinal needle. This procedure has several advantages over those mentioned. (1) Often no general anesthesia will be found necessary, especially in multiparas. Morphia and scopolamine will suffice. At the most nitrous oxide and oxygen are sufficient. (2) No dilatation of the cervix beyond that required to introduce the needle, and therefore no prolonged labor is necessary. The procedure, therefore, does not add a long labor to the dangers of an already overstretched lower segment. (3) The maneuver can be performed by house officers and general practitioners, the men who still deliver most women. Finally, the method can be used on Catholic patients.

At a previous hospital staff meeting in March, 1939, when one of us (O'C.) reported a rupture of the uterus caused by an attempt at internal podalic version in a case of hydrocephalus, the method of Wilson[12] was suggested. This maneuver is applicable to Catholic patients. It was decided by both of the authors to treat the next case of hydrocephalus on our service or in private practice by intraventricular tap with a spinal needle per vaginam, rather than abdominally as recommended by Wilson. During the discussion, the Rev. Fr. Donald McGowan, the superintendent of the hospital, felt that if these procedures did not have as their purpose direct infanticide and did not kill the fetus, there would be no objection from the standpoint of Catholic ethics. It was decided to write to Wilson in order to find out if the tapping produced fetal death. His reply seemed to us conclusive. He states:[13] "In those cases in which the fetal heart is heard when the head is on the pelvic floor, perforation is done to ensure the fetal death, and to facilitate extraction of the head." Later, Moore[14] stated a Catholic viewpoint clearly: "The operation of craniotomy involves two stages: (a) perforation of the skull; (b) complete destruction of the cerebral contents." He goes on to say: "If the second stage of the operation is omitted and the physician attempts to effect delivery with as little loss of cerebral substance as possible and does all he can to save the life of the child, he is no longer making direct attempt to kill the child but in certain rare instances in which delivery may be otherwise impossible, he will be doing all he possibly can do to save the lives, both of the child and of the mother."

For those patients in whom the cervix is difficult to expose, or where the head cannot be brought within the reach of the needle per vaginam, tapping and drainage of the ventricle through the abdominal wall as advocated by Wilson[12, 13] is suggested. The latter uses the procedure as a routine. His method may also be the procedure of election with trained obstetricians or in the rare case of hydrocephalus in a seriously ill patient, such as a Class III cardiac.

CONCLUSIONS

1. We believe that the simplest and safest method of treatment for hydrocephalus when it presents by the vertex is intraventricular tap and drainage per vaginam.

2. Intraventricular puncture abdominally as practiced by Wilson is recommended whenever introduction of a spinal needle through the cervix is difficult or inadvisable.

3. We believe that either of these procedures is superior to the recommendations in current texts, all of which require rather deep general anesthesia, more than a minimum of obstetric training and experience, and some of which are not without danger to the mother.

4. Intraventricular tap and drainage are permissible with Catholic patients.

The writers express their appreciation to the Reverend Francis B. Driscoll, Sister M. St. Clare, O.S.S., Sister M. Bonaventure, O.S.S., and Augustin W. McGarry, M.D.

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Chiray, M. M., Maschas, H., Mollard, H., and Baumann, J.: Spastic Colitis and Ovarian Disturbances, Presse méd. **48**: 881, 1940.

The authors discuss the various pathogenetic theories of primary chronic spastic colitis in women. The review resolves itself eventually into a somewhat lengthy reevaluation of two suggested conceptions. The etiologic factor may be found primarily in the intestinal tract *per se* or secondarily in ovarian hormonal aberrations. They note that chronic spastic colitis is not uncommonly found to be associated with such conditions as sterility, thyroovarian dyscrasias and varying degrees of more general symptoms, such as neurasthenia, neuralgias, myalgias, and generalized malaise.

The writers observe that the association of chronic spastic colitis and ovarian dysfunction appears to be more than coincidental. They were successful in treating both of the above symptom complexes with sex hormones. They used the estrogenic drugs, corpus luteum, and male hormone to secure relief for their 5 patients. These clinicians conclude that the sex hormones may play a role in the physiologic equilibrium of the intestinal tract.

Clair E. Folsome

A CASE OF UNRUPTURED TUBAL PREGNANCY DIAGNOSED BY GYNECOGRAPHY*

IRVING F. STEIN, M.D., CHICAGO, ILL.
(From the Michael Reese Hospital)

THE inconstancy of the clinical picture of unruptured tubal pregnancy is universally recognized. If there is one reliable and dependable sign of this condition, it is the extreme tenderness found on palpation of the affected tube. When this sign is absent, as in the case reported below, the diagnosis is likely to be especially difficult. In this case, gynecography[1] (pneumoroentgenography) proved to be of such positive assistance in diagnosis that it assumed the deciding role. As this method of diagnosis is not commonly employed by the profession in ectopic pregnancy, and in order to call attention to its value in clinical diagnosis, this case report is made.

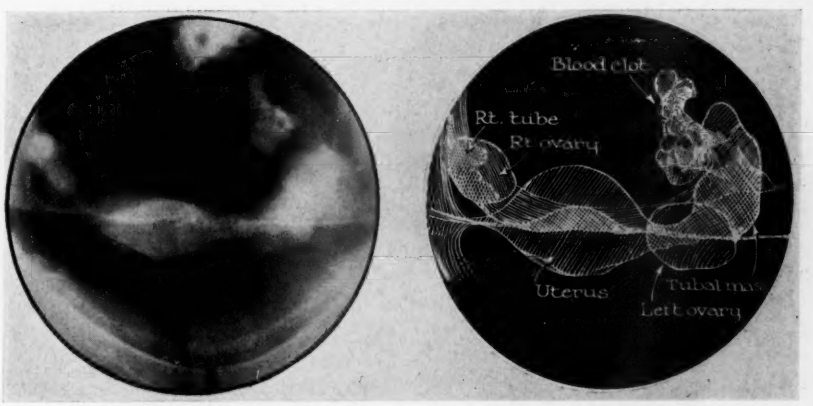

Fig. 1.—Unruptured tubal pregnancy (gynecography).

CASE REPORT

M. W., a 24-year-old woman, nullipara, married 2½ years, was first examined in the office Oct. 2, 1941. The history was that the menses, which had been regular 28-day type, 5-day moderate flow since the onset at age 11, were one week late in September, appearing on September 17, and then reappearing on September 26, accompanied by sharp left abdominal pain. The patient stated that contraception had been practiced until one month ago, and then intentionally interrupted. She gave a vague history of renal calculus last year.

Physical Examination.—The breasts were large, soft, but showed no typical evidence of pregnancy change. The uterus, normal in size, was retroverted and mobile. Both adnexa were *free from tenderness* and palpable swelling. The cervix was nulliparous, closed, and contained a

*Presented at a meeting of the Chicago Gynecological Society, October 17, 1941.

clear mucous secretion. Rectovaginal-abdominal examination revealed the same findings.

Pulse was 84; color, normal; blood pressure, 130/88; weight, 152 pounds. Urine showed a trace of albumin; no sugar; pH, 5.0; epithelial cells and occasional red blood cells in the sediment.

Tentative Diagnosis.—Suspected tubal pregnancy. Re-examination was advised in a few days when pregnancy tests were to be carried out. She was warned of possible danger and symptoms which might occur.

Four days later, October 6, she had an acute attack of pain in the left side during the night, and was sent to the Michael Reese Hospital by a neighborhood physician who also thought she had an ectopic pregnancy. Upon arrival at the hospital at 3:00 A.M., however, her pain had subsided and the abdomen was neither tender nor rigid. There was slight pink vaginal discharge. Examination revealed her pulse 92 (varied from 84 to 96), blood pressure 110/70, hemoglobin 70 to 80 per cent, red blood count 3,740,000, white count 14,000, and the urinalysis negative.

Bimanual examination revealed the same findings as in the first instance, complete absence of adnexal tenderness or mass, which made the diagnosis of tubal pregnancy questionable. The differential diagnosis to be made was: (1) tubal pregnancy, (2) intrauterine threatened abortion, (3) ureteritis or calculus, and (4) left corpus luteum cyst.

Various diagnostic procedures were considered and a decision was made to obtain a pelvic pneumogram using the transabdominal route (CO_2 inflation). The film (Fig. 1) accurately revealed the affected tube, showing the changes characteristic of tubal pregnancy. The shadow of both ovaries, uterus, and unaffected right tube appeared normal.

Laparotomy was performed through a Pfannenstiel incision, and an unruptured tubal pregnancy was removed. The similarity between the shape and size of the involved tube and the image which it produced on the x-ray film was indeed striking.

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310 South Michigan Avenue

THECA CELL TUMOR*

W. C. Danforth, M.D., Evanston, Ill.

IN RECENT years tumors of the Graafian follicle have been the subject of much study. While tumors of pure granulosa or theca type are not common, those in which granulosa cells predominate are far more numerous. In a recent report, Curtis stated that 33 theca cell tumors have been reported and added one to that number. In my service, a tumor predominantly composed of theca cells has been seen recently. In January, 1941, a private patient, aged 58 years, entered the hospital for the removal of a large pelvic tumor. Her menopause had occurred six years earlier. At 32 years of age a laparotomy had

*Presented at a meeting of the Chicago Gynecological Society, October 17, 1941.

been done. She believed that this was for pelvic inflammatory disease. No bleeding had been noted at any time since the menopause.

Examination disclosed a firm mass which extended four inches above the symphysis, somewhat irregular in shape, and movable. It was thought to be a myoma of the uterus.

Operation was carried out on January 31. A large, asymmetric, firm, pale left-sided ovarian tumor was found. The pedicle was quite short. The right ovary was normal. The uterus was of normal size. The left ovarian tumor was removed and a total hysterectomy done, leaving the adnexa on the right side. Recovery was uneventful.

The uterus contained a small intramural myoma, and there was a definite endocervicitis. The ovarian tumor weighed 635 Gm. The external surface was smooth and glistening. Sectioned surfaces were firm to slightly cystic, pale gray white, irregularly mottled yellow. The fluid in the cystic area was sticky.

Sections from the ovarian tumor revealed some areas composed of small, fusiform or stellate cells. The nuclei were small and fusiform In some regions there was considerable pink intercellular substance which formed plaques. These areas were undergoing cystic degeneration. Some sections displayed numerous small cells, resembling theca cells which contained fat. This fat had an affinity for sudan III and stained black after fixation with osmic acid. Foot's modification of Bielschowsky's silver stain for fibrous tissue revealed a fine mesh of fibrous tissue surrounding the thecalike cells with a very delicate reticulum.

No hormonal stimulus was exerted by this tumor. In the series studied by Traut and Marchetti, a lack of hormonal influence was found in 28.3 per cent. Hormonal stimulus may vary with the age of the tumor and the proportion of cells of the theca type which a tumor contains. In this case the tumor, which was in an early stage of its development, had probably lost any hormonal effect which it might have had at an earlier stage of its growth. The large proportion of cells of the theca type would also lessen its endocrine activity.

It is difficult to draw an absolute line between the two types of tumors of the Graafian follicle, but those in which cells of the theca type predominate and those rather rare ones, which are of pure theca type, are benign. Of the granulosa group, it is estimated roughly that 10 per cent are malignant. In dealing with tumors of the theca type, the treatment need not be radical, a simple excision of the ovary in which the tumor is found being sufficient.

636 CHURCH STREET

Richard, A.: Plastic Removal of Redundant Abdominal Wall Tissue, Zentralbl. f. Gynäk. **64**: 1542, 1940.

The author describes a trapezoid incision which he favors over the usual elliptical incision, as it allows more extensive removal of tissue and easier coaptation of skin margins. An incision slightly concave upward is made from one anterior iliac spine to the other. At a suitable distance above, another shorter parallel curved incision is made. The ends are connected by two short diagonally placed incisions completing the trapezoid.

R. J. WEISSMAN

Special Article

GRADUATE EDUCATION IN OBSTETRICS*

The Seminar System as Developed in Philadelphia

Philip F. Williams, M.D., Philadelphia, Pa.

A SYSTEM of graduate education in obstetrics has been developed in Philadelphia in recent years through the medium of four committees. These committees study the various causes and surrounding circumstances of maternal deaths, stillbirths, fetal deaths, and premature births. The meetings, conducted as open seminars for the medical public, have been found to be an excellent type of extramural graduate education.

We had found that institutes or seminars conducted in county medical societies in Pennsylvania were unsatisfactory: on one hand from indifference of many members and, on the other, through difficulty in obtaining suitable teams of speakers to conduct these institutes. This was not due to a lack of obstetric qualifications as much as to their inability to interpret the problems of local physicians and to teach general practitioners.

Locally, intramural graduate education in obstetrics, through residencies and fellowships, with close clinical contacts in dispensaries, wards, and delivery rooms, has been most successful for the younger men. The Graduate School of Medicine at the University has offered for many years an excellent didactic and clinical course for men who have had a general obstetric experience and who desire polishing up for specialization.

The shorter intramural courses of one and two weeks in maternity hospitals have proved successful for graduates of moderate experience who wish to obtain new ideas and techniques for their practice, as well as to get a general freshening up on modern hospital methods. This system has been efficiently conducted in Philadelphia and Pittsburgh by the Commission on Maternal Welfare of the State Medical Society in conjunction with the Bureau of Maternal and Child Health of the State Health Department.

In order to obtain a full and all the year round discussion of various phases of obstetrics, we continued a closed analysis of maternal deaths as an open cooperative program between the hospital obstetric staffs of Philadelphia and the County Medical Society. Each month for seven years a representative of the various hospitals has voluntarily brought a complete record of any maternal death occurring in his hospital. A suitable abstract of the case on a printed folder is presented for our files. A discussion follows, with particular emphasis as to how such cases could be handled in the future to avoid the factors which influenced the fatal outcome.

*Read at the Thirteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, October 2-4, 1941, New Orleans, La.

As these discussions went on month by month, it was apparent that much bad obstetrics was being practiced. Corrective measures were taken to prevent unnecessary obstetric surgery or operative maneuvers in the hospitals by unqualified men. Keeping in mind the particular point of operative ability, most of the hospitals have rejudged their courtesy staffs, and have more clearly defined the privileges of the junior staffs. The hospitals accepted, in full or modified form, a detailed set of regulations governing the conduct of their maternity divisions. Chiefly, these cover rules for obligatory consultations and regulations for technique in labor, delivery rooms, and the nursery. Obligatory consultation before cesarean section in a large number of our hospitals has led, in my opinion, to a marked decline in the mortality from the operation, even though the incidence of the operation has shown a slight increase.

Through available funds, copies of such procedure books as that of the American Hospital Association and the regulations for maternity hospitals of the Chicago and New York Boards of Health, as well as various publications of the State Department of Health, and the Children's Bureau, have been sent to attending obstetricians of the hospitals. When the Committee on Maternal Welfare of the County Medical Society has made a specific recommendation regarding some particular situation, a mimeographed copy is sent to a large list of interested physicians.

In the monthly discussion of case reports much stress was laid for a time upon the presence and nature of avoidable factors. To avoid too much emphasis in an open meeting concerning responsibility and preventability, the hospital staffs have been asked to decide such points. Their decisions are noted upon the case study folder. This request necessitated the institution of individual hospital obstetric conferences. Mortality reports must be discussed at these conferences prior to the case presentation at the analysis meeting at the County Medical Society. The final presentations are made now by the interne or resident because of their manifested interested and intimate knowledge of the case history. A vote of the analysis group is taken regarding the preventability and responsibility of the death, when there is a general disagreement with the decision of the hospital staff.

As a result of these monthly seminars an obstetric conscience has been developed in Philadelphia.

Much of the material in the abstract files has been used in preparation of papers read before medical meetings. Assignments of topics to teams of younger men has served to cement their interest and act as stimuli in furthering graduate education in other groups.

As a consequence of this system of graduate education in obstetrics in Philadelphia, there has been a drop in the maternal mortality rate. This has fallen from 68 puerperal deaths per 10,000 live births in 1931, the year the study began, to 23 such deaths in 1940, a reduction of 67 per cent.

Since it was realized that fetal and neonatal salvage was germane to such a study, two committees were formed to investigate the stillbirths and neonatal deaths in Philadelphia. The first committee was organized under the auspices of the Obstetrical Society of Philadelphia. The second committee was developed under the auspices of the Department of Health, in order to bring the facilities of the Bureau of Vital Statistics

more closely into this work. These committees met separately for one year, studying their respective cases. Realizing their problems were largely similar, they merged meetings. It has not been possible to present for discussion every stillbirth and neonatal death. All cases are reviewed and tabulated by subcommittees. Four cases, with as far as possible the same basic cause, are presented by each committee at the monthly seminar. At a recent meeting 4 stillbirths and 4 neonatal deaths were reviewed, where in each instance the mother had been a diabetic.

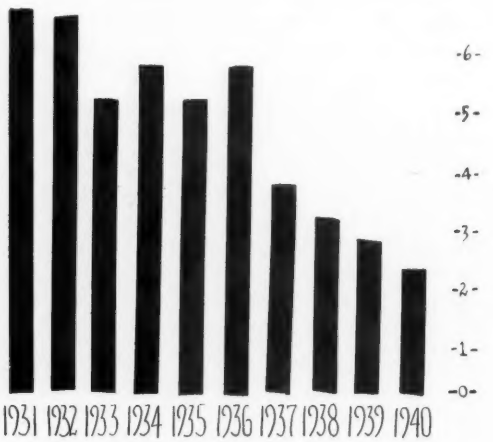

Fig. 1.—Puerperal (maternal) deaths per 1,000 live births.

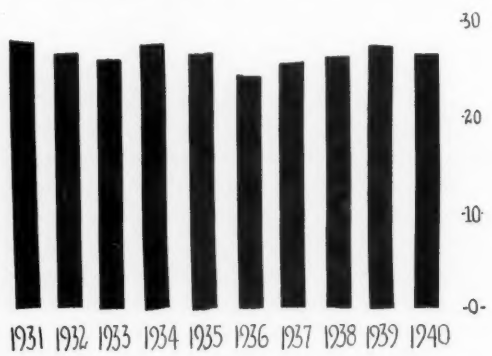

Fig. 2.—Neonatal deaths per 1,000 live births.

At another meeting, each death discussed had been in association with breech presentation, and, at yet another meeting, each mother had been extremely obese, two hundred pounds or more in weight. During the final fifteen minutes of each joint session of these two committees, a prepared résumé of the principal topic of the meeting, the basic cause of death, is given by a physician to whom the topic has been assigned previously. The pediatricians have shown a marked interest in these meetings, while the hospital pathologists have been helpful in discussing autopsy protocols. It was noted that a 50 per cent increase in autopsies in stillbirths and neonatal deaths occurred from the first to the third year of these studies.

The development of this second phase of our work broadened the base of the program on graduate education in obstetrics. The problems of prenatal care have been brought out more clearly. The study of the immediate neonatal period has been intensified. This expansion has resulted in reducing the stillbirth rate almost 40 per cent during the past few years.

A similar decrease has not been noted in the neonatal death rate. A review of the first two years' statistics of the neonatal study revealed that in one manner or another prematurity was the basic cause of death in over 50 per cent of such cases.

It was felt necessary to deal with prematurity as a special problem. Consequently, a new group has been formed to develop educational efforts along the lines of both cause and care of prematurity. Realizing that too many central meetings would probably nullify our efforts, the group interested in this problem has been made a traveling clinic. Each month the meetings are held in a different hospital. The obstetric and

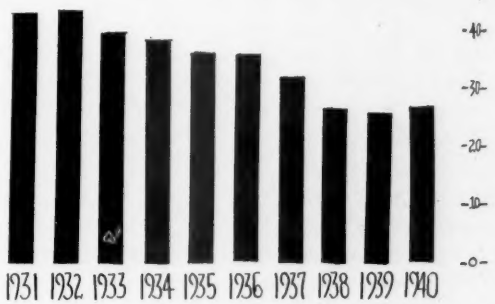

Fig. 3.—Stillbirths per 1,000 total births.

pediatric staffs of the hospitals, in turn, present the statistics of their premature births during the preceding twelve months, discuss the causes, their method of treating prematures, and demonstrate their equipment and personnel. But one such meeting is required to determine the qualifications of a hospital as a premature station.

These four committees form the basis of our extramural graduate education in obstetrics in Philadelphia. Continuously they present to the specialist, general practitioner and interne, the various problems and situations in obstetrics which call for mature judgment and skillful clinical technique. The discussions serve as a stimulus for more efficient study of cases in office practice and hospital clinic. There can be no doubt that the compulsory consultation service in hospitals has had a far reaching effect in providing timely and efficient therapeutic and operative help as well as avoiding much meddlesome midwifery.

Similarly, the problems of the fetus have been brought into sharp focus and the interest of the pediatric group has brought in line greater efforts to conserve the life of the newborn. Although the last committee, on the premature, has been in operation less than a year, its influence is being manifested in a widespread quickening of interest in this problem.

Graduate education in obstetrics, either intra- or extramural, will always be sought by the man who desires to improve his knowledge,

clinical experience and technique. Such a physician will get some good from almost any type of educational opportunity offered him.

Seminars at short intervals, voluntarily and cooperatively produced, can provide excellent instruction in the various phases of obstetric practice for men working in this specialty. A sustained interest has been maintained in our locality, with an average monthly attendance of over one hundred for our seven years. As evidence of the success of such a system of graduate education in obstetrics, we have noted a significant reduction in the maternal mortality rate; a moderate lessening of stillbirths and a determined effort on the part of all concerned to improve further our vital statistics.

The organizations of these committees signified no originality on our part. The analysis of maternal deaths follows closely the pattern of the Ohio Hospital Obstetric Society. The Stillbirth Study Committee uses the form employed by the Children's Bureau in their nationwide stillbirth study. Since the publication of their list of causes of stillbirths, we have used that manual in our classification. The Neonatal Mortality Committee uses the form popularized by Dr. Bundesen and the Chicago Board of Health. Finally, the Study of Prematurity, a joint committee of obstetricians and pediatricians, is along the same lines as that instituted about a year ago by the New York Board of Health.

DISCUSSION

DR. J. C. LITZENBERG, MINNEAPOLIS, MINN.—We are just over the threshold of another great movement in obstetrics and gynecology and that movement must become nation wide. Papers such as we have had this morning are good examples of what is being done in awakening the obstetric conscience throughout the country. The report of the Association of American Medical Colleges published last year, with an extensive survey under the direction of Dr. Robin Buerki, shows the fine efforts being made in certain places, the desultory efforts in other places, and the absence of all effort in too many localities.

We have come to distinguish between the terms "graduate education" and "postgraduate education" in obstetrics. Graduate education is at the level of graduate study in any other department of the University leading to an advanced degree, while postgraduate education is not of such advanced type, but is intended to keep the medical profession acquainted with the problem of maternal welfare. Dr. Lapham spoke about the great number of physicians that had been taking such courses under various plans. Dr. Buerki's survey emphasized not the number of physicians that were taking these courses but the overwhelming number of physicians that were not taking them.

They found in this survey that the gross results as measured by maternal morbidity and deaths or early deaths of babies are an exact measure of the work that is being done in the localities where these educational plans are being carried out. We have learned from Dr. Williams this morning what the effect of such efforts has been in Philadelphia. That is probably the best example of the seminar method. He claimed no originality but I think they are approaching perfection in developing this method.

We as a Society do not need to worry about advanced graduate education. Medical educators are taking care of that, although they have not reached the limit of the possibilities. In this discussion today, however, we are not considering the training of specialists, but are considering what can be done to keep the medical profession on a high level of practice.

This Society should be the one to encourage this great movement because we represent more states than any other society, 28 of the 48 states. For many years in Iowa, Wisconsin, Minnesota, and other midwestern states we have been undertaking this work. Minnesota had a mortality rate of 6.0 when we began in 1915 to have maternal mortality statistics by the U. S. Census Bureau. The national rate was 7.0 including the southern districts where the negro problem and the economic situations are such great factors. Our maternal mortality rate for the state of Minnesota last year had dropped to below 2.0 The Health Commissioner of Minneapolis told me recently that in the city of Minneapolis where the University is located the maternal mortality is 1.3. Iowa, Wisconsin, and North Dakota together with other states where postgraduate courses are given have the lowest maternal mortality in the United States.

In Minnesota and, I presume, in the other states success has been due to cordial cooperation of the Minnesota State Medical Society, the Minnesota Obstetrical and Gynecological Society, the State Department of Health, the University of Minnesota and the Minnesota Maternal Welfare Committee. These organizations work together and every effort that is made along these lines is done after consultation and with cooperation. For example, our extension courses are given on the University campus in a building built for that purpose and are under the direction of a full-time director of postgraduate medical education of the Medical School. The University faculty with some additions from other members of the State society do the teaching. They are trained teachers, which we think is very essential.

We have tried various methods of sending out teachers to various parts of the state, but now we are conducting all our courses on the campus. Those courses are given two or three times a year on different phases of obstetrics and pediatrics. This movement is so big that the universities will have to organize a new department of postgraduate medical education with a full-time director.

The secret of the whole thing is cooperation of all agencies that may be factors; the state medical society, the local and state obstetric and gynecologic society, the health department, the State university, and the maternal welfare committee. When you get forces like these working together you can lower your mortality as much as 70 per cent, as demonstrated by Dr. Williams in Philadelphia, by Minnesota, Iowa, Connecticut, and in many states where any of these different efforts for postgraduate medical education have been undertaken.

DR. VIRGINIA E. WEBB, NEW ORLEANS, LA.—The papers of Dr. Williams and of Dr. Lapham have both brought out the key point in postgraduate education, that is, the use of actual case histories as the basis for teaching. This type of material cannot fail to interest the men who are actually responsible for the results obtained and the men who are confronted with similar problems in their own practices.

Dr. Williams has pointed out the problems encountered in Pennsylvania in conducting institutes or seminars, in particular the indifference of many members of the society and the difficulty of obtaining suitable teams of speakers to conduct these institutes because of the special ability needed to teach general practitioners. In the type of program which Dr. Lapham has outlined, it is very necessary that the consultants be well chosen in order that they be able to hold the interest of the hospital staffs and visiting physicians.

I would like to emphasize the recommendations which Dr. Lapham has made that the consultants conduct meetings at which obstetric procedures are discussed, morbidities and mortalities are analyzed and pathologic reports presented. It seems to me that the methods which have been used in Philadelphia could be very easily

used as a basis for preparation of reports on maternal mortalities. Every effort should be made to induce willingness on the part of the staff members to discuss frankly the mortalities and morbidities with the consultant acting as an impartial referee.

Dr. Lapham's point with regard to the study program, including pediatric consultation, is well taken. Again, the method of study of stillbirths and neonatal deaths used in Philadelphia might well be worked into the program carried on in the hospitals. In future plans for Louisiana it is anticipated that this will be done.

Recognizing the unusual local situation of having six Charity Hospitals in our State, through which a program of postgraduate education might be conducted, the plan outlined by Dr. Lapham was undertaken. Concrete results as have been pointed out by Dr. Williams are not yet measurable, but it is hoped that within a very few years the program will bear fruit in reducing maternal and infant mortality in the State of Louisiana.

DR. HOWARD H. CUMMINGS, ANN ARBOR, MICH.—Twelve years ago in the State of Michigan, Dr. James Bruce was appointed director of postgraduate medicine of the University of Michigan, and for the past six years I have had the privilege of working with him. I want to report the response of the Michigan physicians to this plan. Our effort is a cooperative one, shared in by the University of Wayne, the University of Michigan, the Michigan State Medical Society, and the Department of Health.

A survey made twenty-five years ago in our state showed that 17 per cent of the doctors of Michigan had taken some postgraduate work throughout their medical career. Last year, using what we call the Michigan plan, over 55 per cent of the doctors of Michigan had taken postgraduate work.

In the fall during the month of October and in the spring during the month of April, these men have the work taken to them. In the lower peninsula they will have to drive not more than fifty miles to get the work, and next year we will open five centers in the northern peninsula. For four days we thus bring to the doctors of our state the progress made in the various fields of medicine and over 2,500 doctors are coming every year to attend these lectures. As far as obstetrics is concerned, we always have an obstetric subject presented in both the fall and spring sessions.

In addition Dr. Norman Miller and Dr. Norman Kretzschmar instruct doctors with large obstetric practices who come to the University and take two weeks refresher courses. We have in Detroit also a course for men who attend the courses in their vicinity.

The work is growing rapidly. We have 4,500 doctors belonging to our State Society and over 55 per cent are taking postgraduate work every year. This must be reflected to the people of Michigan in an improvement not only in obstetric practice but in other medical sciences.

DR. E. D. PLASS, IOWA CITY, IA.—Dr. Litzenberg made a statement which must be challenged to some extent. He said, I believe, that graduate education was on a firm foundation and in no danger. There is one element of danger in the situation with which we should be familiar so we can combat it.

The objective of graduate education in obstetrics and gynecology in this country at present is to qualify young men for the Board examination so they may be given a diploma of the Board. Last spring there developed in the Advisory Committee for Medical Specialties the concept that the training period of these graduate students should be resolved into two equal periods of eighteen months, one interval

given over to a study of the basic sciences and the other eighteen months to clinical instruction. Most of us will agree that basic science instruction is worth while. So also most of us will agree that eighteen months is not a sufficient time to give even a brilliant young man adequate clinical training. Fortunately it was not adopted. Apparently there are certain individuals on the Advisory Committee who are trying to develop graduate education in obstetrics and gynecology just as it is in biology or psychology or some of the other nonmedical disciplines. I think we should be cautious and should discourage any effort to decrease the clinical training of these young men to any such extent. In the final analysis, the objective of the Board, as I see it, is to assure the development of adequately trained clinical obstetricians and gynecologists, so that the women of the country may have better care than they would otherwise have. I believe this trend toward overemphasis on the basic sciences may defeat that really broad objective.

DR. WENDELL H. STADLE, BATTLE CREEK, MICH.—I would like to talk about the awakening effort in the small town. I am from Battle Creek, Michigan, where we deal with a great many rural cases. The plan we have in conjunction with the Kellogg Foundation is one of the best to improve rural obstetrics I have heard of in a long time. We are interested in the records of all of the four types of cases which Dr. Williams told you about, stillbirths, neonatal deaths, maternal deaths, and deaths of the child occurring one month after delivery. We go so far as to send out into the rural areas a councilor who will go to the family to find out their circumstances, and whether or not there was a reason why the woman was not sent to a hospital. We have gone to the doctor who delivered the woman and questioned him. We have taken all the hospital records, and have brought a report back to the committee of doctors who study the case to determine whether the fault was due to lack of good medical attendance, hospitalization, consultation, nursing care, financial, or social problems, in the same way as is done in the larger cities. We have learned that it is time to go to the man out in the country and to give him every help. You cannot force him to do things, but you can bring to him things that are interesting.

DR. RUDOLPH W. HOLMES, UNIVERSITY, VA.—Many factors tend to better obstetric work which already have been reflected in a lessened morbidity and mortality the country over. Among these is the enormous increase in the use of hospital facilities for parturients, for the hospital obstetric technique is superior to anything which may be employed in the home. The registration of good hospitals by the American Medical Association, and the recognition by the College of Surgeons of those hospitals which have demonstrated peculiar fitness for their work have been invaluable.

In Chicago forty years ago about half of all deliveries were conducted by midwives, while in 1938 only 548 births were managed by midwives. In this same year in Hartford, Conn., 99 per cent of all births were hospital births; in Philadelphia the rate was 84.4 per cent. In 1939 the registered hospitals of the country could have taken care of 74 per cent of all national births if they were fully occupied and with unrecognized hospitals approximately 80 per cent of all births could have been hospitalized. Yet but 48.0 per cent were actually controlled in hospitals.

DR. HIRAM W. KOSTMAYER, NEW ORLEANS, LA.—In the final analysis this question goes back to the character of the doctor, to his interest in the program and to his integrity. If our medical schools through their undergraduate curriculum, their internships and their residencies are turning out a class of men who will not have to be kept educated but will keep themselves educated, perhaps the necessity

for postgraduate or graduate medical training other than leading to the advanced degrees, may in the future become unnecessary.

At present, however, it seems to me of paramount importance to reach the physicians, more particularly perhaps in the rural districts but in many of the urban districts as well. At Tulane we have tried to reach the so-called general practitioners in the rural communities in one of several ways. The two important ones are intramural programs and extramural or extension teaching programs. At each session at Tulane we have in attendance considerably over 200 men and women physicians. They are not confined to the immediate geographic surrroundings but come from the four points of the compass of the United States. Finding, however, that there are a good many physicians who either could not or would not come into Tulane for postgraduate medical training we have been conducting for some years our postgraduate extramural training. This has been confined to the southern states but not always to obstetrics and pediatrics.

DR. LAPHAM.—Dr. Williams' paper demonstrated a proved method by which maternal and infant mortality can be decreased. This is probably one of the best long-term maternal programs that has ever been presented, and I hope that everyone here will be stimulated to put into operation such a program if it is not already developed in his community.

Society Transactions

CENTRAL ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS

Thirteenth Annual Meeting, October 2, 3, and 4, 1941

The following papers were presented:

Clinical Application of Ergonovine During the Third Stage of Labor. Dr. A. W. Diddle (by invitation), Iowa City, Ia. (For original article, see page 450.)

Diaphragmatic Hernia in the Newborn Infant. Drs. John A. Haugen and C. J. Ehrenberg, Minneapolis, Minn. (For original article, see page 502.)

The Relation of Inhalation Analgesia and Anesthesia to Asphyxia Neonatorum. Dr. Curtis J. Lund (by invitation), Madison, Wis. (For original article, see page 365.)

Radium in the Treatment of Uterine Bleeding Caused by Benign Lesions. Drs. Lawrence M. Randall, Sim B. Lovelady and Fletcher S. Sluder (by invitation), Rochester, Minn. (For original article, see page 377.)

The Use of Uterine Packs Impregnated with Sulfanilamide. Drs. Harley E. Anderson, Herman L. Gardner, M. F. Gunderson, and J. M. Slack, Omaha, Nebr. (For original article, see page 410.)

Syphilis in Obstetrics. Dr. E. D. Plass, Iowa City, Ia. (For original article, see page 484.)

Nutritional Edema in Pregnancy. Dr. R. E. Arnell, and W. F. Guerriero, New Orleans, La. (For original article, see page 467.)

A Review of Seventy-five Cases of Eclampsia. Drs. G. S. McClellan, W. D. Strayhorn and P. M. Densen, Nashville, Tenn. (For original article, see page 493.)

Premature Rupture of the Membranes. Drs. John H. Morton, C. S. Peabody, John Newdorp, and Fred L. Adair (by invitation), Chicago, Ill. (For original article, see page 422.)

Gynecographic Aid in the Diagnosis of Ectopic Pregnancy. Dr. Irving F. Stein, Chicago, Ill. (For original article, see page 400.)

A Study of One Hundred and Fifteen Cases of Ruptured Ectopic Pregnancy. Dr. W. O. Johnson, Louisville, Ky. (For original article, see page 437.)

Nutrition Study in Pregnancy. Dr. Philip F. Williams, Philadelphia, Pa. Guest speaker.

Postgraduate Hospital Teaching Program through Consultation Service in Community Hospitals. Dr. Maxwell E. Lapham (by invitation), New Orleans, La.

Graduate Education in Obstetrics. Dr. Philip F. Williams (by invitation), Philadelphia, Pa. (For original article, see page 528.)

Clinical Evaluation of Equine Gonadotropin. Dr. Laman A. Gray, Louisville, Ky. (For original article, see page 387.)

Office Curettage for Prolonged and Resistant Puerperal Bleeding. Dr. Phil C. Schreier, Memphis, Tenn.

Complete Laceration of the Perineum and the Repair. Dr. Joseph W. Kelso, Oklahoma City, Okla.

Effect of Lymphogranuloma Venereum on Pregnancy, Labor, and the Fetus. Drs. C. Leon Wilson (by invitation) and H. Close Hesseltine, Chicago, Ill. (For original article, see page 459.)

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF OCTOBER 17, 1941

The following case reports were presented:

A Case of Unruptured Tubal Pregnancy Diagnosed by Gynecography. Dr. Irving F. Stein. (For original article, see page 525.)

Theca Cell Tumor. Dr. W. C. Danforth. (For original article, see page 526.)

The following paper was presented:

Pregnancy in the Syphilitic Mother. Dr. S. J. Benensohn. (For original article, see page 508.)

Correspondence

Early Ligation of Cord

After reading the editorial by Dr. Harry Bakwin, on "Depriving the Infant of Its Placental Blood," in the October, 1941, issue of the JOURNAL, I would state that I am in accord with its contents. But, I feel that we should not overlook other factors, which might mean either life or death, a normal child or one perhaps showing brain tissue involvement. We should also take into consideration the type of labor, that is, whether or not it has been prolonged, with the head pounded against the perineum, or where there is a hematoma.

In all types of breech delivery and all types of forceps delivery, there is always the danger of a tear in the tentorium cerebelli, and in these instances one would want a decreased amount of fluid in the blood stream.

This specific group of cases should receive further study relative to depriving the infant of some of its placental blood.

Usually, following these particular types of cases, I give from 10 to 20 c.c. of maternal blood, into the gluteal region or under the scapula. It tends to hasten coagulation in the baby's blood, thereby checking any bleeding in that particular region and avoids intercranial pressure which brings about respiratory embarrassment. This is kept up for a period of from three to five days. In this way one can build up the loss of red corpuscles and also the hemoglobin. In many of these cases one notices most particularly respiratory embarrassment due to bleeding in the tentorium cerebelli. Soon after the administration of the blood, this tends to clear up. The same applies to a child that may become spastic after delivery.

A. HERBERT KANTER, M.D.

Columbus, Ohio
December 12, 1941.

To the Editor:

Though late ligation of the cord leads to an increase in the blood volume of the newborn, it is hardly likely that this would affect the bleeding which results from the tearing of tissues. Under such circumstances the use of vitamin K or, better, one of the substitutes, is indicated to bring the coagulability of the blood within the normal range. There is no reason to use blood subcutaneously or intramuscularly, since this does not increase the coagulability of the blood as well as vitamin K; indeed it is doubtful whether it increases it at all. Red blood cells, given parenterally, except by the intraperitoneal route, do not enter the blood stream.

HARRY BAKWIN, M.D.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Toxemia of Pregnancy

Hofbauer, J.: New Orientation on the Etiology of the Toxemia of Pregnancy, West. J. Obst. & Gynec. **49**: 615, 1941.

The writer presents a succinct account of new concepts regarding the pathogenesis especially of late toxemia, dealing particularly with the biologic significance of three well-defined principles, namely histamine, the posterior pituitary hormone and acetylcholine.

In his opinion, increasing information in regard to interaction of these three pharmacologic agents during pregnancy provides hope for clarification of certain fundamentals in the etiology of toxemia.

From a consideration of the pivotal position of the liver in the detoxification of products of hormonal secretion, in the storage of glycogen, plasma protein, and water metabolism, the view crystallizes that in the prenatal period efforts toward preservation of integrity of liver function as a guard against possible toxemia may be of decisive importance.

HUGO EHRENFEST.

Penfold, W. J.: On the Nature of Eclampsia, Med. J. Australia **11**: 198, 1941.

The author states that there are signs of acidosis in eclampsia, the specific acid in excess being lactic acid. This probably accounts for the absence of glycogen in the liver. In eclampsia the synthesis of lactic acid to glycogen in the liver is defective. One has to deal with a derangement of the Cori cycle produced by infection or toxemia, so that lactic acid is not promptly and efficiently converted into glycogen. It accumulates in the body and gives the coma of acidosis. The author places great emphasis on infection as a theoretical cause in eclampsia.

The author deems it necessary to make good the defect in the alkali reserve which occurs in eclampsia. The alkali must not be given in excess, since the patient might pass from the convulsions of eclampsia to those of alkalosis. He concludes that eclampsia is an acute sarcolactic acid intoxication occasioned by a large production of the substance within the body, and by an interruption of its disposal by the synthesis of glycogen, which depends upon the presence of some infection.

WILLIAM BERMAN.

Page, E. W.: Effect of Eclamptic Blood on Urinary Output and Blood Pressure of Human Recipients, J. Clin. Investigation **17**: 207, 1938.

Page undertook to determine whether the transfer of 400 c.c. of blood from patients with severe pre-eclampsia or eclampsia to normal pregnant women would have any effect on the blood pressure, urinary output, and symptomatology of the recipient and to discover in eclamptic blood traces of posterior pituitary in excess

of the amount that might be present in normal blood. Thirty-seven determinations of antidiuretic effects together with blood pressure curves were done on 28 patients. As little as 0.01 unit of solution of posterior pituitary may be readily detected on suitably prepared normal human test subjects. Transfusions of 500 c.c. of blood from normal donors do not result in a significantly altered blood pressure or urinary output in the recipient, although the results suggest the presence of traces of posterior pituitary in normal blood. If small amounts of solution of posterior pituitary are added to human blood in vitro and allowed to stand for from thirty to sixty minutes before transfusion, a definite antidiuretic response may be obtained in the recipient. If large amounts of solution of posterior pituitary are given to donors prior to the withdrawal of blood, no definite antidiuretic response can be obtained in the recipient, indicating a rapid elimination or destruction of the hormone from the circulating blood stream. When amounts of 400 c.c. of blood are rapidly transferred from patients with eclampsia or severe pre-eclampsia to normal pregnant women, the recipients do not show any rise in blood pressure, interference with diuresis or untoward symptoms. The results do not confirm the contention that there is a toxic substance in toxemic blood or support the theory that there is a hypersecretion of the posterior pituitary in eclampsia.

J. P. GREENHILL.

Yamada, K.: A Study of the Relationship Between the Origin of Eclampsia and Allergy, Japanese J. Obst. & Gynec. 23: 2, 1940.

Yamada experimenting with rabbits found histologic differences in the pregnant animals which were sensitized to blood serum from eclamptic women but were not present in the animals sensitized to blood serum from noneclamptic women. This he attributes to allergy. Furthermore, he found that an antigen which produced a strong shock reaction was to be found only in the blood serum and placentas of eclamptic patients. The author, therefore, firmly believes that eclampsia has its origin in allergic changes.

J. P. GREENHILL.

Cope, Cuthbert Leslie: Excretion of Pregnandiol in Toxemia of Pregnancy, The Lancet 2: 158, 1940.

Previously published reports have indicated a greatly reduced excretion of pregnanediol glucoronidate in the urine of patients with toxemia of pregnancy. A study by the author of a series of ten cases of toxemia does not confirm this claim. During the last month of normal pregnancy, 30 to 90 mg. of pregnanediol glucoronidate is excreted daily with a mean figure of 55 mg. In the toxemic group the excretion varied from 28 to 55 with a mean of 39.4 mg. In one pregnant patient with chronic nephritis no pregnanediol was excreted.

CARL P. HUBER.

Ch'ing-shan, Lu: Total 24-Hour Urinary Excretion of Estrogens in Normal and Toxemic Pregnancies, Chinese M. J. 59: 131, 1941.

The daily urinary excretion of estrogens was studied in normal pregnancies as well as in cases of pre-eclampsia, eclampsia, chronic nephritis, mild toxemia, and vomiting of pregnancy.

Except in cases of hyperemesis, a decrease in the excretion of estrogens in the urine was found in all the toxemic pregnancies.

A lowering of the urinary estrogen was also observed in a patient receiving corpus luteum during pregnancy.

C. O. MALAND.

Peckham, Charles H.: The Effect of Syphilis and Its Treatment on the Incidence of Toxemia of Pregnancy, Am. J. Syph., Gonor. & Ven. Dis. **25**: 280, 1941.

This is a report of 13,742 consecutive deliveries at the Johns Hopkins Hospital. Antisyphilitic treatment administered to pregnant syphilitic women during pregnancy does not increase the incidence of toxemias of pregnancy.

C. O. MALAND.

Setzer, O.: Dependency of Eclampsia Upon Climatic Factors, Zentralbl. f. Gynäk. **64**: 972, 1940.

The author studied meteorologic conditions obtaining during 129 attacks of eclampsia. A change in weather either to colder or warmer was noted at the onset of 75 per cent of cases. A change to cold was found in 54 per cent more cases than a change to warm weather. Relative humidity was high at the onset of eclampsia in 68 per cent of cases. An increase in the incidence of eclampsia was found in April, May, and June and in the months in which there were many changes from cold to warm weather. Barometric pressure as a factor was not considered in this study.

R. J. WEISSMAN.

Lennon, G. Gordon: Eclampsia—A Statistical Review, Brit. M. J. **1**: 944, 1938.

A comprehensive study and report of eclampsia in the northeastern area of Scotland is given. Colon lavage, gastric lavage, and venesection (for blood pressure over 160 mm. Hg) are done. Also 1 gr. of thyroid extract is given daily to further diuresis. Occasionally, veratrone, ½ c.c. intramuscularly, is used as an alternative for venesection. Membranes are ruptured for labor induction if the patient is at or near term. When labor has already begun, it is terminated as quickly as possible. Conservative measures are employed only if the patient is unduly far from term and if she responds well to treatment.

The incidence of eclampsia in the Aberdeen Hospital over a period of five years was 1.59 per cent. The incidence was 18 per cent higher in the winter months from October to March than from April to September; 73.77 per cent of the cases occurred in either first or second pregnancies, 65 per cent up to the age of 30 years without any deaths. The mortality rate over 30 years was 28.6 per cent. Antipartum eclampsia was as common after 30 years of age as before. However, the post-partum type was more common (77 per cent of cases) before the age of 30. There was a striking difference between the mortality rates for towns (5.71 per cent) and for the county (15.4 per cent).

The maternal mortality rate for this series was 9.84 per cent. This figure was doubled in illegitimate pregnancies. The fetal mortality rate, including neonatal loss, was 39.34 per cent.

F. L. ADAIR AND JOHN A. HAUGEN.

McKelvey, John L.: Remote Vascular Lesions of the Toxemias of Pregnancy and Their Clinical Significance, The Journal Lancet **51**: 35, 1941.

The author gives consideration to the role of pregnancy in the production of arteriosclerosis and points out that pregnancy always advances the lesion. In some cases pregnancy may produce a speedy progression of the disease with ultimate destruction. Of all the known exacerbating agents in hypertension, pregnancy is the most certain and severe. Not only does the pregnancy affect the arteriosclerosis but the pregnancy may be prejudiced by the toxemia, the major effect lying in the production of the condition known as ablatio placentae. It is felt that the

persistence of a systolic blood pressure of 140 mm. of mercury and/or a diastolic pressure of 90 mm., and/or albuminuria allows a diagnosis of arteriosclerosis. Whether the hypertension is primary or secondary to the toxemia is only of academic interest. It is stated that at the Johns Hopkins Hospital in a ten-year period following a diagnosis of arteriosclerotic toxemia, 25 per cent of the patients died. It is the author's opinion that if early recognition of the lesion and appropriate sterilization were carried out, the dreadful remote mortality of the disease might be somewhat lessened.

WILLIAM BERMAN.

Heynemann, Th.: Eclampsia and Its Precedent Conditions, Deutsche med. Wchnschr. **66:** 757, 1940.

Heynemann believes that there is a storage of metabolic products in the placenta which affects the gravida in eclampsia and its related states. Early diagnosis and treatment are essential as the prognosis is seven times better in the pre-eclamptic states. An albumin-, fat-, and salt-poor diet with 1 liter of fluid intake is recommended. Prophylactically a diet is given in which vegetables and fruits largely replace meats and fats. Patients are hospitalized as soon as definite indication of disease appears. In considering increase of blood pressure, the individual's usual pressure should be considered rather than the reading per se. Diagnostic helps in experienced hands are: (1) Reduction of the response to galvanic stimulation of the median nerve. Alterations in the response have prognostic value; (2) Retinal vascular spasm; (3) Alterations of capillary flow as noted in nail folds. Venesection for control of hypertension should be carefully controlled by constant blood pressure readings to avoid collapse.

R. J. WEISSMAN.

McNeile, Lyle G., and Page, Ernest W.: The Personality Type of Patients with Toxemias of Late Pregnancy, Am. J. M. Sc. **197:** 393, 1939.

A method used by a previous worker in the study of nonpregnant individuals with essential hypertension has been utilized to study the personality types of women with normal pregnancies, and with pregnancies complicated by pre-eclamptic toxemia, eclampsia, glomerulonephritis, or essential hypertension.

The results indicate that only those women with essential arteriolar hypertension (as a group) differ significantly from the normal in having personalities characterized by an increased psychomotor activity.

Further correlations are shown between the diagnosis and the age, parity, height, weight gain with pregnancy, and family history. A classification based on the probable origin of the hypertension is suggested for use.

The relationship between the hypertensive personality and the late toxemias of pregnancy with its value in differential diagnosis is discussed.

J. THORNWELL WITHERSPOON.

Sakler, B. R.: Eye Changes in Pregnancy, Ohio State M. J. **36:** 522, 1940.

The ophthalmoscope should be considered a valuable adjunct in the modern management of the toxemias of pregnancy because hypertensive, angiospastic, toxemic, retinal changes appear early. It is generally conceded that toxemic cases with normal ocular fundi make a complete recovery. The visual prognosis in toxemic patients who develop peripheral retinal changes is on the whole surprisingly good. A diagnosis of optic neuritis, retinitis, or retinal detachment, presents a definite indication for the immediate termination of the pregnancy, in an effort to safeguard the future health and vision of the mother.

J. P. GREENHILL.

Irving, F. C.: A Study of Five Hundred Consecutive Cases of Pre-eclampsia, Canad. M. A. J. **137:** 40, 1939.

The author summarizes 500 cases of pre-eclampsia seen in a two-year period at the Boston Lying-in Hospital. Of these 397 were mild with hypertension of mild degree and no more than a slight trace of albumin in the urine, 248 were primiparas and 27.8 per cent of the multiparas had had pre-eclampsia in a previous pregnancy.

The leading signs and symptoms were edema in 71.6 per cent, headache in 41.8 per cent, vomiting in 27.45 per cent, and visual disturbances in 27.0 per cent. Blood chemistry studies were of little clinical value. Patients with a systolic blood pressure above 150 or a diastolic pressure above 100 were hospitalized.

Treatment consisted of bed rest, restriction of the fluid intake below the output of the preceding twenty-four hours. A milk diet of 1,200 c.c. or less was given for the first three days followed by a low salt, low protein diet of 1,378 calories. Magnesium sulfate was given for catharsis.

Of the pregnancies, 39 per cent were terminated artificially, 8 per cent by cesarean section, but only 8 of the 40 cesarean sections were performed because of the toxemia. The fetal mortality was 2.6 per cent in 194 pregnancies terminated between thirty-two and thirty-six weeks, and 5.9 per cent in 252 patients delivered at from thirty-six to forty weeks of gestation. The gross fetal mortality was 6.9 per cent for the group, which is only 0.6 per cent greater than for the hospital population during the same period.

Five patients developed convulsions, all post partum. There was one maternal death following low segment cesarean section performed because of a contracted pelvis after twenty-four hours of trial labor. Death was due to general peritonitis. The maternal mortality was 0.2 per cent.

CARL P. HUBER.

Furtado, Alfonso H.: The Treatment of Eclampsia by the Method of Stroganoff, Rev. de gynec. e d'obst. (Rio de Janeiro) **2:** 386, 1938.

The author, reviewing in detail and recommending Stroganoff's method and statistics, reports a series of 15 cases; 11 of the patients were treated conservatively with no mortality, while in those treated surgically the maternal mortality rate was 8.3 per cent.

MARIO A. CASTALLO.

Guerriero, Wm., Leidenheimer, Henry, and Zander, Edwin: An Analysis of 220 Cases of Eclampsia from Charity Hospital at New Orleans, New Orleans M. & S. J. **94:** 68, 1941.

The authors base their conclusions upon 220 cases with a fetal mortality of 41 per cent and a maternal mortality of 8.6 per cent. The management of eclampsia involves three considerations: (1) its prevention by adequate prenatal care; (2) the termination of pregnancy if pre-eclampsia cannot be controlled; (3) if eclampsia has definitely set in it should be treated primarily, with delivery delayed until the convulsions have been controlled. Toward the end of the period covered in this study, the incidence of eclampsia and the mortality rate decreased due to better prenatal care. Cesarean section was never performed with eclampsia as the indication per se.

EUGENE S. AUER.

Naeslund, John: Hyperemesis Gravidarum, Upsala läkaref. förh. **45:** 285, 1939.

Although 62 per cent of the pregnant women attending the author's clinic during 1937 and 1938 suffered vomiting, only 0.6 per cent of that total attendance fell

in the hyperemesis gravidarum group. He briefly reviews the various theories of the causation of hyperemesis.

He develops a theory of the cause of pregnancy toxicosis, particularly in relationship to hyperemesis and abruptio placentae, which is dependent on the assumption that substances from the ovum enter the mother's blood stream and produce a condition of allergy. The significance of the paternal contribution to the ovum in this connection is emphasized. The author then turns specifically to the blood. The results of investigating the blood groupings in 236 mothers and children and some fathers in relation to nausea, vomiting, and albuminuria of pregnancy indicate that the serious cases are strikingly more numerous when the mother and child differ in blood grouping. Evidence is offered of the presence of fetal blood in the maternal circulation. Allergy studies by the method of intracutaneous injection are described in detail and lead to the conclusion "that substances are sometimes to be found in the body of the pregnant woman which react to injections of blood from the fetus or the father."

A number of histories are reviewed of patients in whom relief was obtained after all other methods had failed, by the use of repeated intramuscular injections of from 1 c.c. to 20 c.c. of the husband's blood.

CLAUDE J. EHRENBERG.

Brandstrup, Ebbe: Some Problems Concerning the Pathogenesis and Treatment of Hyperemesis Gravidarum, Acta obst. et gynec. Scandinav. **19**: 376, 1939.

In Denmark, hyperemesis each year costs the lives of six women, necessitates 30 to 40 therapeutic abortions, and causes illness and serious inconvenience in over 4,000 women. Treatment with large doses of suprarenal cortex was tried in 11 cases of hyperemesis. In four of the cases the condition was aggravated, necessitating therapeutic abortion, while improvement was seen in the remaining cases. Hence it appears that suprarenal cortex is not a specific remedy for hyperemesis, and the author's results speak strongly against the hypothesis that insufficiency of the suprarenal cortex might be the primary cause of hyperemesis.

The author assumes that hyperemesis is brought about by an abnormal reaction of the organism to the greatly increased hormone production that is a normal feature of pregnancy.

Secondarily, the development of hyperemesis is largely dependent upon psychic factors. As the third factor in the pathogenesis a state of inanition develops, in which severe damage to the liver and the central nervous system is due to a rapid fall in glycogen and to vitamin deficiency, probably caused by the inanition under the special hormonal conditions present in the pregnant organism. In keeping with this view of the pathogenesis, the proper conservative treatment will consist in a sedative, psychic, and restorative therapy aimed to counteract the vomiting and its consequences. Restorative therapy consists in administration of sodium chloride, water, glucose, insulin, and vitamins. The future will show whether suprarenal cortex is to be established as an effective remedy in the restorative therapy. If conservative treatment fails, interruption of the pregnancy is necessary.

J. P. GREENHILL.

Walther, P.: The Treatment of Gastric Pain and Vomiting of Pregnancy by Means of Histidine, Bull. Soc. d'obst. et de gynéc. **27**: 190, 1938.

Walther used a 4 per cent solution of the monochloride of histidine in 50 cases for nausea and vomiting of pregnancy, and heartburn. Injections are given every day or every second day depending upon the severity of the symptoms. There

are no general reactions from this therapy and only a slight burning sensation locally. The author warmly recommends this medication because he has obtained spectacular results with it.

J. P. GREENHILL.

Westman, A.: Hyperemesis Gravidarum, Acta. obst. & gynec. Scandinav. **20:** 203, 1940.

In a period of three years, 66 cases of hyperemesis were observed at the Lund Women's Clinic. The treatment generally adopted consisted of abstinence from food, injections of glucose and insulin for one or two days and then an abundant supply of salt by mouth. In 28 women prolan determinations of the urine were made and an increase was found in the majority of the cases. However, there was no parallelism between the severity of the disease and the increase in the amount of prolan. Abortions were induced in the severe cases.

In the discussion of this paper, Ahlstrom said that in his entire career, which included observation of 56 cases of hyperemesis, he had never performed an abortion nor had he observed a death from hyperemesis. He has treated all his cases by psychotherapy with the aid of bromides.

J. P. GREENHILL.

Items

American Congress on Obstetrics and Gynecology

St. Louis, Missouri, April 6 to 10, 1942

The general features of the program for the coming Congress may be announced as follows:

The morning sessions will be divided into two periods from 9:30 to 11 and 11 to 12. The more formal presentations will appear in the first period.

Monday morning at 11 o'clock there will be a general "Obstetric Information Please," based on the well-known quiz program and presided over by a moderator and four experts. This will be repeated on Wednesday morning, for shock and hemorrhage, and Friday, on economics. Clinical conferences on genital infections will be held Tuesday morning at 11 and Thursday morning on "How Not to Treat Carcinoma." During the afternoons various groups will present formal programs devoted to nursing, public health, and hospital administration, among which will be certain combined programs.

A special feature of this Congress will be a daily consultation service at 3:30. About 50 nationally known physicians will make themselves available for fifteen-minute consultations through a registration system by individual practitioners who may desire such advice in their specific problems.

Round table discussions will also be arranged by the section chairmen.

Practical demonstrations are scheduled in the scientific exhibit area on manikin deliveries, home care technique, and blood transfusions. Details of programs of other sections will appear shortly.

Further information is available at the Central Office of the Congress at 650 Rush Street, Chicago. Hotel reservations should be made directly and at an early date. Physicians, nurses, public health administrators, educators, and hospital administrators are urged to send in their registration fee of $5.00.

Postgraduate Courses in Obstetrics at Chicago Lying-in Hospital

Five postgraduate courses in obstetrics, each of four weeks' duration, will be offered at the Chicago Lying-in Hospital between January 12 and June 6, 1942. These are sponsored by the Illinois State Department of Health and the Children's Bureau of the U. S. Department of Labor. The features of the program consist of observations on current managements of normal and abnormal states of the pregnant, parturient, and puerperal patient. Lectures, demonstrations, clinics, and other teaching means augment the operating room and birth room observations, and ward round discourses. The course is run on a non-profit basis. A deposit of $25.00 is required on registration, $10.00 of which is refunded at the completion of the course. All the members of the department participate in giving the courses. Additional information and application blanks may be obtained by request from Postgraduate Course, Department of Obstetrics and Gynecology, 5848 Drexel Avenue, Chicago, Illinois.

American Board of Obstetrics and Gynecology

The general oral and pathologic examinations (Part II) for all candidates (Groups A and B) will be conducted at Atlantic City, N. J., by the entire Board, from Wednesday, June 3, through Tuesday, June 9, 1942, prior to the opening of the annual meeting of the American Medical Association.

Formal notice of the time and place of these examinations will be sent each candidate several weeks in advance of the examination dates.

Candidates for *reexamination* in Part II must make written application to the Secretary's Office before April 15, 1942.

As previously announced in the Board booklet, this fiscal year (1941-1942) of the Board marks the close of the two groups of classification of applicants for examination. Thereafter, the Board will have only one classification of candidates, and all will be required to take the Part I examinations.

The Board requests that all prospective candidates who plan to submit applications in the near future request and use the new application form which has this year been inaugurated by the Board. The Secretary will be glad to furnish these forms upon request, together with information regarding Board requirements. Address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pa.

Erratum

In the article by Z. J. R. Hollenbeck and P. J. Reel entitled "The Use of Stilbestrol in the Management of the Menopause," page 332, February issue, the cuts are incorrectly placed. Fig. 1 has the caption for Fig. 2, and vice versa.